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RICHTER-ANSCHÜTZ

THE CHEMISTRY OF THE CARBON COMPOUNDS

RICHTER-ANSCHÜTZ, THE CHEMISTRY OF THE CARBON COMPOUNDS

Volume One:—THE ALIPHATIC SERIES

Volume Two:—THE ALICYCLIC SERIES AND NATURAL PRODUCTS

Volume Three:—THE AROMATIC CARBOCYCLIC SERIES AND ORGANIC FREE RADICALS

Volume Four:—THE HETEROCYCLIC SERIES

THE CHEMISTRY OF THE CARBON COMPOUNDS

BY

VICTOR VON RICHTER

EDITED BY THE LATE

PROF. RICHARD ANSCHÜTZ

VOLUME II

THE ALICYCLIC COMPOUNDS AND NATURAL PRODUCTS

TRANSLATED FROM THE XIITH GERMAN EDITION (COMPILED
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PREFACE

This book is a translation and revision of Volume II/1 of the twelfth edition of Richter-Anschütz' *Chemie der Kohlenstoffverbindungen*, which was published in German in 1935. The revision has been carried out in the following fashion: the authors of the various sections added to, and in some parts re-wrote, their contributions to the German edition, and the whole was then translated. Dr. Millidge was responsible for almost all the translation, but some of the earlier parts were carried out by Dr. A. Finkelstein and Dr. N. Rydon. I then worked through the translation and produced the text which appears in this book. I cannot claim to have carried out as complete a revision as I should have wished; the time which a college tutor has available is quite insufficient for such a task. My aim was to extend the number of references quoted in the text, particularly to special monographs, so as to make the book of greater use as a source of information for English speaking people, to make some mention of recent work on the subjects discussed and to remove inconsistencies between the various sections. It has been impossible to consult the authors of the German text upon every point that arose, and so the responsibility for the final form of the text is mine alone.

The sections dealing with the *Digitalis* saponins, the cardiac glycosides and the toad poisons have been entirely re-written by Professor F. Reindel. In the final revision of the vitamin section I have had the valuable assistance of Professor A. R. Todd, to whom my warmest thanks are due. I must also express my thanks to Dr. F. Rochussen for the trouble he has taken in helping me with the printing and proof-reading. He has read the whole volume through, both in manuscript and in two proofs, and has made many useful suggestions. Finally, my thanks are due to Dr. A. Finkelstein who was of help in the preliminary arrangements and in the earlier sections which he translated, and to Dr. S. G. P. Plant who assisted in the revision of those sections.

One new feature of the present English edition of this work is that, with the exception of a few non-chemical journals, the references are given to the original papers and not to the *Zentralblatt*, and that the names of the authors have been added to all the references.

Brasenose College, Oxford, October 1938.

T. W. J. Taylor.

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LIST OF ABBREVIATIONS

Ac. Belge	Académie royale de Belgique, Bulletin de la Classe des Sciences et des Lettres.
Acta physicochim.	Acta physicochimica (U.S.S.R.).
Acta phytochim.	Acta phytochimica (Japan).
Am.	Journal of the American Chemical Society.
Am. J. med. Sci.	American Journal of Medical Sciences.
Am. J. Physiol.	American Journal of Physiology.
Am. Pharm.	American Journal of Pharmacy.
Anal. Esp. Fis. Quím.	Anales de la Sociedad Española Fisica y Química.
Anat. Rec.	Anatomical Record (Philadelphia).
Angew.	Angewandte Chemie.
Ann.	Annalen der Chemie (Liebig's).
Ann. Brux.	Annales de la Sociéte scientifique de Bruxelles.
Ann. chim.	Annales de Chimie.
Ann. chim. phys.	Annales de Chimie et de Physique.
Ann. Comb.	Annales des Combustibles.
Ann. Physik	Annalen der Physik.
Ann. Rep. Chem. Soc.	Annual Reports on the Progress of Chemistry (Chemical Society, London).
Apoth.-Ztg.	Apotheker-Zeitung.
Arch. Entw.-mech.	Archiv fur Entwicklungsmechanik der Organismen.
Arch. exper. Path. Therap.	Archiv für experimentelle Pathologie und Pharmakologie.
Arch. farm. sperim.	Archivio di Farmacologia sperimentale e Scienze affini.
Arch. Gynäk.	Archiv für Gynakologie.
Arch. Path. Pharm.	Archiv für experimentelle Pathologie und Pharmakologie.
Arch. Pharm.	Archiv der Pharmazie.
Arch. Scienze biol.	Archivio die Scienze biologiche.
Atti R. Accad. Lincei	Atti della Reale Accademia dei Lincei. Classe di scienze.
Beitr. chem. Physiol Path.	Beitrage zur chemischen Physiologie und Pathologie.
Belge	Bulletin de la Société chimique de Belgique.
Ber.	Berichte der Deutschen chemischen Gesellschaft.
Biochem. J.	Biochemical Journal.
Biochem. Z.	Biochemische Zeitschrift.
Boll. chim. farm.	Bolletino chimico-farmaceutico.
Bull.	Bulletin de la Société chimique de France.
Bull. chem. Soc. Japan	Bulletin of the Chemical Society of Japan.
Bull. Pin	Bulletin de l'Institut du Pin.
Bull. Soc. Chim. biol.	Bulletin de la Société de Chimie biologique.
Bureau Standards J. Res.	Bureau of Standards Journal of Research = Journal of Research of the Bureau of Standards.

C.	Chemisches Zentralblatt.
C. r.	Comptes rendus hébdomadaires des Séances de l'Académie des Sciences.
C. r. Soc. biol.	Comptes rendus hébdomadaires des Séances de la Société de Biologie.
Can. J. Res.	Canadian Journal of Research.
Chem. and Ind.	Chemistry and Industry.
Chem. News	Chemical News.
Chem. Rev.	Chemical Reviews.
Chem. Weekbl.	Chemisch Weekblad.
Chem.-Ztg.	Chemiker-Zeitung.
Compt. rend. Acad. Sci. URSS.	Comptes rendus de l'Académie des Sciences de l'USSR.
Current Sci.	Current Science, Bangalore.
Deut. med. Woch.	Deutsche medizinische Wochenschrift.
Erg. Physiol. biol. Chem. Erg. Physiol. exp. Pharmakol.	Ergebnisse der Physiologie, biologischen Chemie und experimentellen Pharmakologie.
Fermentforschg.	Fermentforschung.
Gazz.	Gazzetta chimica italiana.
Helv.	Helvetica chimica Acta.
Ind. Eng. Chem.	Industrial and Engineering Chemistry.
J.	Journal of the Chemical Society (London).
J. agr. Res. Washington	Journal of Agricultural research (Washington).
J. agr. Sci.	Journal of Agricultural Science.
J. Am. med. Assoc.	Journal of the American Medical Association.
J. Am. pharm. Assoc.	Journal of the American Pharmaceutical Association.
J. Bioch.	Journal of Biochemistry (Japan).
J. biol. Chem.	Journal of Biological Chemistry.
J. chem. Soc. Japan	Journal of the Chemical Society of Japan.
J. Dyers	Journal of the Society of Dyers and Colourists.
J. exper. Med.	Journal of experimental Medicine.
J. Indian chem. Soc.	Quarterly Journal of the Indian Chemical Society.
J. Indian Inst. Sci.	Journal of the Indian Institute of Science.
J. Pharm. Belge	Journal de Pharmacie de Belgique.
J. pharm. chim.	Journal de Pharmacie et de Chimie.
J. pharm. Soc. Japan	Journal of the Pharmaceutical Society of Japan (Yakugakuzasshi).
J. Pharmacol.	Journal of Pharmacology and Experimental Therapeutics.
J. phys. Chem.	Journal of physical Chemistry.
J. Physiol.	Journal of Physiology.
J. pr.	Journal fur praktische Chemie (Neue Folge).
J. Soc. chem. Ind. Japan	Journal of the Society of Chemial Industry, Japan.
J. Soc. chem. Ind. London	Journal of the Society of Chemical Industry, London.
J. Univ. Bombay	Journal of the University of Bombay.
J. Washington Acad.	Journal of the Washington Academy of Sciences.
Kautschuk	Kautschuk, Berlin.
Klin. Woch.	Klinische Wochenschrift.
Lancet	The Lancet.
Lincei.	Rendiconti della Reale Accademia dei Lincei.
Medicine	Medicine, Baltimore.
Med. Australia	Medical Journal of Australia, Sydney.
Mem. Coll. Sci. Kyoto	Memoirs of the College of Science, Kyoto Imperial University.
Mo.	Monatshefte für Chemie.

N.	Naturwissenschaften.
Nachr. Ges. Wiss. Göttingen	Nachrichten von der Gesellschaft der Wissenschaften zu Göttingen.
Naturw. = N.	
Pat. = Patent.	
Pflügers Arch.	Archiv fur die gesamte Physiologie des Menschen und der Tiere.
Pharm. J.	Pharmaceutical Journal.
Pharm. Weekbl.	Pharmaceutisch Weekblad.
Phil. Trans.	Philosophical Transactions of the Royal Society (London).
Philippine J. Sci.	Philippine Journal of Science.
Physiol. Rev.	Physiological Reviews.
Proc.	Proceedings of the Chemical Society, London.
Proc. Imp. Acad. Tokyo	Proceedings of the Imperial Academy of Japan.
Proc. Indian Acad. Sci.	Proceedings of the Indian Academy of Sciences.
Proc. Royal Irish Acad.	Proceedings of the Royal Irish Academy.
Proc. Roy. Soc.	Proceedings of the Royal Society, London.
Proc. Royal Soc. N. S. W.	Proceedings of the Royal Society of New South Wales.
Proc. Soc. exp. Biol.	Proceedings of the Society for Experimental Biology and Medicine.
Rec.	Recueil des Travaux chimiques des Pays-Bas.
Rev. Chim. ind.	Revue de chimie industrielle, Paris.
Sch. & Co. } Ber. (German ed.)	Schimmel & Co., (Halb-) Jahresbericht.
Schimmel } Report (Engl. ed.)	Schimmel & Co. (Semi-) Annual Report.
Sci. Pap. Inst. phys. chem. Res. Tokyo	Scientific Papers of the Institute of Physical and Chemical Research, Tokyo.
Sci. Rep. Tohoku	Scientific Reports, Tohoku Imperial University.
Skand. Arch. Physiol.	Skandinavisches Archiv fur Physiologie.
Trans. Faraday Soc.	Transactions of the Faraday Society.
Z. anal. Chem.	Zeitschrift fur analytische Chemie.
Z. angew. Chem.	Zeitschrift fur angewandte Chemie.
Z. Biol.	Zeitschrift für Biologie.
Z. exper. Med.	Zeitschrift fur experimentelle Medizin.
Z. exper. Path. Therap.	Zeitschrift für experimentelle Pathologie und Therapie.
Z. f. Chem.	Zeitschrift fur Chemie.
Z. Krist.	Zeitschrift fur Kristallographie und Mineralogie.
Z. med. Chem.	Zeitschrift für medizinische Chemie.
Z. physikal. Chem.	Zeitschrift für physikalische Chemie.
Z. physiol. Chem.	Zeitschrift fur physiologische Chemie (Hoppe-Seyler).
Z. Unters. Lebensm.	Zeitschrift fur Untersuchung der Lebensmittel.

TABLE OF YEARS

in which the volumes of the more important journals appeared. For most of the other journals both the year and the volume number are given in the text.

Abbreviation	Title	First published	Vol. per year	1890	1900	1910	1920	1930
				Volume numbers				
Am.	Journal of the American Chemical Society	1879	1	12	22	32	42	52
Ann.	Liebig's Annalen der Chemie	1832	4–8	256 to 260	310–313	372 to 377	420–421	477–484
Arch. Pharm.	Archiv der Pharmazie	1822	1	228	238	248	258	268
Ber.	Berichte der Deutschen Chemischen Gesellschaft	1868	1	23	33	43	53	63
Biochem. J.	Biochemical Journal	1906	1			5	14	24
Biochem. Z.	Biochemische Zeitschrift	1906	10 to 15			23–29	102–112	217–229
Bull.	Bulletin de la Société chimique de France	1864	2	(III) 3	(III) 23	(IV) 7	(IV) 27	(IV) 47[1]
C. r.	Comptes rendus de l'Académie des Sciences, Paris	1835	2	110	130	150	170	190
Chem. and Ind.	Chemistry and Industry, London	1923	1					8
Gazz.	Gazzetta chimica italiana	1871	1	20	30	40	50	60
Helv.	Helvetica Chimica Acta	1918	1				3	13
Ind. Eng. Chem.	Industrial and Engineering Chemistry	1909	1			2	12	22
J.	Journal of the Chemical Society, London	1841	2[2]	57	77	97	117	—[3]
J. pr.	Journal fur praktische Chemie, neue Folge	1868	2–3	41–42	61–62	81–82	100–101	124–127
Mo.	Monatshefte für Chemie	1880	1–2	11	21	31	41	55–56
Proc.	Proceedings of the Chemical Society, London	1885	1	6	16	26	Discontinued 1914	
Proc.Roy. Soc.	Proceedings of the Royal Society, London	1800	1–4	47–49	66–67	83–84	96–97	126–130
Rec.	Receuil des Travaux chimiques des Pays-Bas	1882	1	9	19	29	39	49
Z. physikal.Chem.	Zeitschrift für physikalische Chemie	1887	5–6	5–6	32–35	69–74	94–96	146-151[4]
Z. physiol. Chem.	Zeitschrift für physiologische Chemie	1877	6–9	14	29–30	64–70	108–111	186–193

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[1] The series number (IV) is omitted in the text. Series (V) begins in 1934.

[2] From 1841 to 1925.

[3] From 1926 the volumes have no number except that of the year.

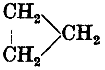
[4] Section B of this journal in 1930 appeared in volumes 6—11.

INTRODUCTION

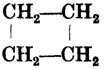
In the first volume of this work the methane derivatives or acyclic carbon compounds containing open carbon chains have been described. The subject matter of the next two volumes comprises organic compounds with closed carbon chains or carbon rings, termed **carbocyclic compounds.** An analogous group is constituted, e.g., by the azocyclic compounds, with a ring consisting exclusively of nitrogen atoms, as was formerly assumed in hydrazoic acid. The carbocyclic compounds are often referred to as **isocyclic** compounds, though this is too general an expression, since it implies any compound containing a ring formed from atoms of one and the same element, whatever that element may be. The carbocyclic compounds must be distinguished from the **heterocyclic compounds,** which contain rings formed partly of carbon atoms, and partly of other atoms.

Both in the acyclic class and in the carbocyclic class the hydrocarbons are regarded as the parent substances from which the other compounds are derived. Saturated carbocyclic hydrocarbons are isomeric with olefins containing the same number of carbon atoms and consist of rings composed of three or more methylene groups. They are called either **cycloparaffins** according to the Geneva convention, by a name formed from that of the corresponding normal paraffin by adding the prefix "cyclo", or **polymethylenes,** distinguished as tri-, tetra- etc. methylenes according to the number of methylene groups in the ring. An older terminology using the name of the isomeric normal olefin and prefixing "R" (ring-olefins) has become obsolete. The term preferred at present is "cycloparaffins". The parent substances constitute the homologous series:

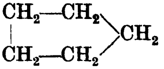
Cyclopropane (trimethylene)



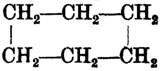
Cyclobutane (tetramethylene)



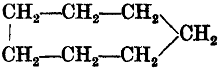
Cyclopentane (pentamethylene)



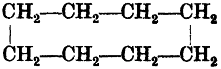
Cyclohexane (hexamethylene)



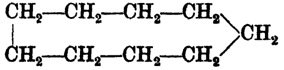
Cycloheptane (heptamethylene)



Cyclo-octane (octamethylene)



Cyclononane (nonamethylene)



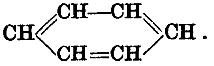
etc.

Cyclohexane or hexamethylene is also called hexahydro-benzene and cycloheptane or heptamethylene is known as suberane.

Just as compounds with two, three or more double bonds can be derived from paraffins, so unsaturated cyclo-olefins can be derived from cyclo-paraffins.

A special importance attaches to the carbocyclic ring of benzene, which is the parent hydrocarbon of the **aromatic substances** or **benzene derivatives,** the most numerous class of organic compounds. *August Kekulé* formulated benzene as a ring of six carbons linked by alternating double and single bonds, i.e. as a cyclo-triolefin.

Benzene (cyclo-hexatriene)



$$\mathrm{CH}\begin{matrix}\diagup\!\!\diagup\mathrm{CH{-}CH}\diagdown\!\!\diagdown\\ \diagdown\mathrm{CH{=}CH}\diagup\end{matrix}\mathrm{CH}.$$

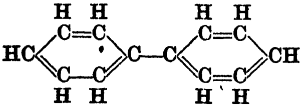
This view, hewever, is incapable of accounting for all the facts which we now know about benzene, and its true structure, which is that of a resonance-hybrid, will be discussed in detail in the appropriate place.

Benzene can be converted into hexahydro-benzene (cyclohexane) by the addition of hydrogen. There is a steady increase in the number of compounds known which are derived from dihydrobenzene (cyclohexadiene) or from tetrahydrobenzene (cyclohexene). These groups together with the cyclohexane derivatives are sometimes called **mononuclear hydroaromatic compounds.** Many substances occurring in nature, the **terpenes** among them, belong to this class.

If the system outlined were strictly adhered to, the homologous cycloparaffin systems, together with the corresponding cyclo-olefins, would be arranged in a sequence based upon the number of carbon atoms in the ring. It is proposed to deviate from this systematic order in two points. The mononuclear 6-ring compounds are, on account of their great number, omitted from the homologous series and described in a section which follows that series. Secondly, the mononuclear aromatic compounds or benzene derivatives are separated from the mononuclear hydroaromatic compounds. The behaviour of the aromatic compounds differs in many respects from that of the aliphatic substances, while the hydroaromatic compounds together with the known carbocyclic substances with 3, 4, 5, 7, 8, 9 or more ring members resemble to a much greater extent the open-chain compounds, either of the saturated, or, if the ring contains doubly bound carbon atoms, of the unsaturated type. Such substances are therefore often spoken of as **aliphatic-cyclic** or **alicyclic, saturated or unsaturated compounds.**

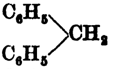
The **polynuclear aromatic compounds** which follow are closely related to the mononuclear aromatic compounds and are derived from the following parent hydrocarbons:

I. Phenyl-benzenes (phenyl = C_6H_5).

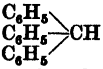


diphenyl; diphenyl-benzenes $(C_6H_5)_2C_6H_4$ etc.

II. Polyphenyl paraffins, olefines, acetylenes, in which the benzene residues are held together by aliphatic hydrocarbon residues:


$\begin{matrix}C_6H_5\\C_6H_5\end{matrix}\!>CH_2$

diphenylmethane


$\begin{matrix}C_6H_5\\C_6H_5\\C_6H_5\end{matrix}\!>CH$

triphenylmethane

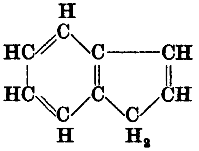
$[C_6H_5\cdot CH_2-]_2$ dibenzyl

$[C_6H_5\cdot HC=]_2$ stilbene

$[C_6H_5\cdot C\equiv]_2$ tolane

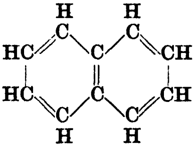
III. Condensed nuclei:

1. Indene group



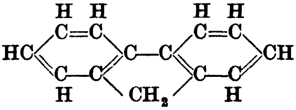
C_9H_8 indene.

2. Naphthalene group



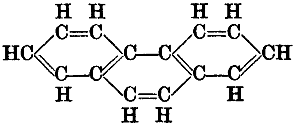
$C_{10}H_8$ naphthalene.

3. Fluorene group



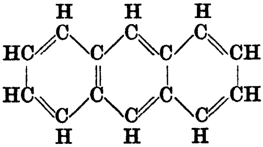
$C_{13}H_{10}$ fluorene.

4. Phenanthrene group



$C_{14}H_{10}$ phenanthrene.

5. Anthracene group



$C_{14}H_{10}$ anthracene.

The more important **free organic radicals**, which are closely related to the polynuclear aromatic hydrocarbons, are described in the following chapter.

The counterparts of polynuclear aromatic hydrocarbons are found in the **polynuclear alicyclic compounds**, which are included after the corresponding mononuclear compounds. The next section comprises the **terpenes** and the **resins**, many of which occur naturally in essential oils.

During the last 20 years, since the eleventh German edition of this book was published, the number of known carbocyclic compounds has grown enormously. The matter has therefore been divided into two volumes in the following way:

Second Volume.

- A. Alicyclic compounds.
  - Ia. Mononuclear 3-, 4-, 5-, 7-, 8- and poly-membered ring compounds.
  - Ib. Mononuclear 6-membered ring, or hydroaromatic compounds. Hydrobenzene derivatives.
  - II. Polynuclear alicyclic compounds.
  - III. Terpenes, resins.
- B. Natural Products.

Third Volume.

- A. Aromatic compounds.
  - I. Mononuclear aromatic compounds, benzene derivatives.
  - II. Polynuclear aromatic compounds.
- B. Organic free radicals.

A. ALICYCLIC COMPOUNDS

BY F. ROCHUSSEN AND K. NIEDERLÄNDER

Many natural products either belong to or are closely related to the class of alicyclic substances; examples are naphthenes and naphthenic acids occurring in petroleum, truxillic and truxinic acids found in cola leaves, pyrethrins in chrysanthemum, many monocyclic terpenes as limonene, phellandrene, and the natural odorants jasmone, muscone and civetone (cf. the sections on pinene, camphor, tropine, ecgonine, pseudopelletierine etc.)

PHYSICAL PROPERTIES

The physical properties of the simpler cycloparaffins are shown below (*Willstatter*, Ber. **40**, 3981). The constants of the hydrocarbons C_{10} to C_{30} will be found in the section on large rings p. 80.

Name	Melting point	Boiling point	d_4^0	n_D
Cyclopropane	gaseous	—33°	—	—
Cyclobutane	liquid	11–12°	0·7038	1·37520
Cyclopentane	,,	49°	0·7635	1·40855
Cyclohexane	+ 6·4°	81°	0·7934	1·4266
Cycloheptane	− 12°	117°	0·8275	1·44521
Cyclo-octane	+ 11·5°	148°	0·850	1·44777
Cyclononane	—	171°	0·785 (?)	1·4328

The **melting points** of the hydrocarbons and ketones of this class oscillate up to C_{15}. The curve rises then to a maximum at C_{18} to C_{19}, drops steeply to a minimum at C_{20} and C_{22} and rises again slowly in the larger rings C_{30} and C_{34}. The maximum and the minimum have also been established in the diketone series (*Ruzicka*, Helv. **13**, 1152; **17**, 82). There is a marked contrast with the aliphatic series, where melting points rise continuously with increasing molecular size, in agreement with the parallel arrangement of zig-zag chains disclosed by X-ray analysis of the paraffins (*Müller*, *Shearer*, J. **123**, 3156; *Katz*, Z. ang. Ch. **41**, 329; *Meyer*, ib. 938; *Ruzicka*, Helv. **9**, 510 note 2).

While the **density** of aliphatic compounds increases regularly with the number of carbon atoms, that of the cycloparaffins and cyclic ketones reaches a maximum and then slowly falls off, approaching the aliphatic curve (*Ruzicka*, Helv. **9**, 499; **13**, 1157; **17**, 79). An explanation is offered by the conception for the solid cyclanes of closed chains in parallel arrangement, which recalls the paraffin structure.

It is interesting to note that the minimum of the yield of the ketones obtained in the thermal decomposition of dibasic acids corresponds with the maximum of the density of the ketones (id. Helv. **13**, 1197).

The **molecular volume** of cyclic compounds, hydrocarbons as well as ketones, is throughout smaller than that of the corresponding aliphatic compounds (id. Helv. **9**, 499). The difference is less marked with the lower than with the higher members. In the smaller rings, carbonyl requires less space than methylene, in the large rings this difference becomes neglegible (id. Helv. **13**, 1164). A thermodynamic relationship between density and the size of the ring has been deduced, based on the space requirements caused by the directed valencies; it leads to the result that the methylene chain must be regarded as occupying roughly a spherical volume up to C_{14}, while from C_{16} upwards the ring is stretched out in one direction with parallel sides (id. Helv. **13**, 1185). These conclusions are supported by the results of X-ray spectroscopy of crystals (*Katz*, Z. Phys. **46**, 392, 19; *Muller*, Helv. **16**, 155), as well as by observations of the spreading of monomolecular films. Further, with the higher molecules (C_{15}) the values of the *parachor* $P = \frac{M}{d} \cdot \gamma^{\frac{1}{4}}$ (where M = molecular weight, d = density, γ = surface tension) approach those of the corresponding aliphatic compounds (*Vogel*, J. **1928**, 2018, *Ruzicka*, Helv. **15**, 8; **16**, 487; *Muller*, ib. **16**, 155, 162):

Ring	2	3	4	5	6	7	8	15	17
P	23·2	16·7	11·6	8·5	6·1	6·0	4·3	−2 (−4·8)	−10·5

In good agreement with these conceptions the mean molecular coefficient of *compressibility* $\beta_{\text{mol.}} = \frac{M}{d} \cdot \beta$ (M = mol. weight, d = density, β = coefficient of compressibility) is nearly constant in the aliphatic series, but decreases markedly with increasing size of ring in the carbocyclic compounds (*Muller*, Helv. **16**, 489).

The **molecular refraction,** computed from the densities and refractive indices, tallies for the six-ring with the theoretical value (vol. I, introduction), ring closure having no effect. The 3-, 4- and 5-rings show positive exaltations, while all higher membered systems are found to have negative exaltations (*Ruzicka*, Helv. **13**, 1162; **14**, 1323; **17**, 81). The ring increments compared to the "normal" 6-ring are

Ring	3	4	5	6	7	8	15
Increment	+ 0·7	+ 0·45	+ 0·04	0·0	− 0.10	− 0·47	− 0·62

Ring closure appreciably depresses the specific exaltation of unsaturated compounds (*Auwers*, Ann. **410**, 299; **415**, 98).

The **molecular refractive index,** the product of refractive index and molecular weight, seems to be of importance as an indication of constitution, as has been shown by the comparison of paraffins with isoparaffins and naphthenes (*Eisenlohr* and *Wohlisch*, Ber. **58**, 1746; *Suida*, Ber. **66**, 1445; *Fajans*, Z. phys. Ch. **99**, 395).

Finally, the Raman spectrum may be mentioned as a method for ascertaining the number and position of double bonds, e.g. in dipentene, terpinene, terpinolene (*Ruzicka*, Helv. **16**, 842; *Gachard*, Bull. Pin **1933**, 97; *Kornfeld*, Z. ang. Ch. **43**, 393), since particular frequencies characterise the single and double linkages.

RING STRAIN, STABILITY AND EASE OF FORMATION

The tetrahedral hypothesis of *Le Bel* and *van't Hoff*, which afforded an excellent explanation of optical isomerism and was the best picture of the general stereochemistry of carbon before cyclic compounds were known, cannot, in its original form, be applied to the latter class of substances. The variations of stability and of ease of formation could not be reconciled with the conception of rigid tetrahedra (*W. Hückel*, Ber. **59**, 2826).

Experience has shown that cyclopropane and cyclobutane rings are opened more readily than the more stable cyclopentane and cyclohexane rings.

Cycloheptane, cyclo-octane and cyclononane rings again are difficult to prepare and are often easily converted into rings of fewer carbon atoms. On the other hand, from the ten-membered ring upwards ease of formation and stability increase again (p. 77). Similar observations have been made with regard to the formation of certain heterocyclic derivatives of aliphatic substances, e.g. of lactones, lactams and dicarboxylic anhydrides. In the section on hydroxy-acids (Vol. I, 414) a hypothesis dealing with the spatial arrangement or configuration of carbon chains was outlined, to explain why γ- and δ-lactones are formed so much more readily than α- and β-lactones.

The **Strain Theory** of *Baeyer* (Ber. **18**, 2278; **23**, 1275; recent references cf. *Ruzicka*, Helv. **9**, 230, 249, 939) attempted to explain the differing stability of the cyclopropane, cyclobutane, cyclopentane and cyclohexane rings. The basic assumption of this theory is as follows: "The four valencies of carbon act in directions which join the centre of a sphere with the corners of a regular tetrahedron enclosed by the sphere; the angle formed by any two of these directions is 109° 28′. The valency direction can undergo a deflection and the strain thus introduced increases with increasing deflection. The assumption of valency forces acting through an angle is ruled out and the magnitude of the angle of deflection is taken as a measure of the strain. In ethylene the two valencies are deflected by equal amounts, until they are parallel; the angle of deflection is in this case one-half of 109° 28′ = 54° 44′. Cyclopropane can be pictured as an equilateral triangle, in which the angle formed by the axes equals 60°; the deflection is therefore $^1/_2\,(109^\circ\,28' - 60^\circ) = +\,24^\circ\,44'$." In the same way the following deflections are computed:

cyclobutane $^1/_2\,(109^\circ\,28' - 90^\circ) = +\,9^\circ\,44'$
cyclopentane $^1/_2\,(109^\circ\,28' - 108^\circ) = +\,0^\circ\,44'$
cyclohexane $^1/_2\,(109^\circ\,28' - 120^\circ) = -\,5^\circ\,16'$
cycloheptane $^1/_2\,(109^\circ\,28' - 128^\circ\,34') = -\,9^\circ\,33'$
cyclooctane $^1/_2\,(109^\circ\,28' - 135^\circ) = -\,12^\circ\,51'$
cyclononane $^1/_2\,(109^\circ\,28' - 140^\circ) = -\,15^\circ\,16'$

The angle of a regular polygon of n sides is $180 \cdot \left(1 - \frac{2}{n}\right)^\circ$. The valency deflection, for instance, in muscone with 15 atoms in the ring (p. 80) would be taken as $\frac{1}{2} \cdot \left(109^\circ\,28' - 180 \cdot \left(1 - \frac{2}{15}\right)^\circ\right) = -\,23^\circ\,16'$. This is nearly the same figure, though of opposite sign, as is found for cyclopropane. These calculations are based on the assumption that in every case the carbon atoms lie all in one plane.

On this view the valency deflection is greatest in dimethylene or ethylene, and thus the strain is greatest. This is the weakest ring, easily disrupted by chlorine, bromine, hydrogen bromide and iodine. Cyclopropane forms addition compounds with more difficulty. Cyclobutane, cyclopentane, cyclohexane do not behave like unsaturated compounds. They are inert towards *halogens* and *hydrogen halides* or, under vigorous conditions, undergo halogen substitution (*Gustavson*, C. r. **131**, 273; *Kishner*, C. 1912 I 2025). Further, by catalytic *hydrogenation* or by reduction with HI and P the double bond is reduced more rapidly than is the ring in a cyclopropane or cyclobutane compound (*Willstätter*, Ber. **40**, 4456; *Zelinsky*, ib. 4743). The *Sabatier-Senderens* method of hydrogenation, e.g., reduces double bonds very rapidly, while the 3-ring does not react below 110° and the 4-ring not below 180°. The same behaviour is shown in catalytic dehydrogenation; the cyclopropane and cyclobutane compounds are rapidly attacked while the 5-rings in n-hexyl-cyclopentane and in naphthenic acids are highly resistant. Oxidising agents, more especially $KMnO_4$, are of little effect on medium-sized rings, while the double bond is extraordinary sensitive.

The **heat of combustion** of simple cycloparaffins decreases in the sequence from cyclopropane to cyclohexane in accordance with *Baeyer's* strain theory (cf. p. 10). The theory predicted a greater ease of formation of the 5-ring than of the 6-ring, which gave occasion to many successful syntheses of cyclopentane derivatives (*Willstätter*, Ber. **28**, 655). The difference in stability of the two rings is, however, not so great as might be expected from the difference in valency deflection. The discrepancy is still more marked in the 7-, 8- and 9-membered rings, which, though increasingly difficult to prepare, are fairly resistant to rupture. For example, cycloheptadecanone is stable even at 400°. Cyclopentane and cyclohexane rings are not attacked by HI and P at even 250°, nor are *Ruzicka's* large ring compounds, e.g. cycloheptadecane. Ketones with 7, 9, 12 and 18 ring members remain unchanged when heated under pressure with conc. HCl (*Ruzicka*, Helv. **9**, 499).

Ozone, according to the observations of *Harries*, acts rapidly on cyclopentene, but less readily on cyclohexene and cycloheptene (Ann. **374**, 303; Ber. **41**, 1701). Similarly, the decomposition of cyclic glycols by lead tetraacetate (*Criegee's* method) proceeds at a much higher rate with 5-ring derivatives, such as hydrindane-diol or acenaphthene-diol, than with cyclohexane-diol, tetralin-diol etc. (*Ruzicka*, Helv. **16**, 216; *Criegee*, Ann. **507**, 180). The rate of *esterification* of cyclic secondary alcohols also decreases on passing from the 5-membered to the 6-membered and further to the 7-membered ring (*Menshutkin*, J. **89**, 1532). When H_2SO_4 acts on cyclic pinacols, the yield of *pinacolin* decreases and that of di-olefin increases with increasing number of ring members (*Ruzicka*, Helv. **14**, 1319). The pinacol of the 5-ring is transformed practically completely into the corresponding spirane, while this ring transformation is only a side reaction with the 7-ring compound, and in 8- and 15-rings does not take place. A similar phenomenon is observed the in the deamination of carbocyclic methylamines by nitrous acid; the lower members react with formation of carbinols and ring expansion, the higher ones chiefly with formation of olefins (id. ib. **9**, 399). Further, both in the reactivity of cyclic *bromides* (*Lovenich*, Ber. **62**, 3084) and the decomposition of *ketone-bisulphite* compounds (*Petrenko*, Ann. **341**, 164) the rates of reaction are slower with the 6-ring than with the 5- and 7-rings.

The **cyclanones** are much more reactive towards hydroxylamine, phenylhydrazine, bisulphite etc. than are their isomers among the aliphatic ketones with a central carbonyl group (id. Ber. **34**, 1702; **39**, 1452). The sequence of reaction velocity towards these reagents is 6-ring > 5-ring > 7-ring (*Ruzicka*, Helv. **15**, 8). The 5-ring ketones react at the same rate as the aliphatic methyl ketones, the 6-ring show a maximum of reactivity, and there is a steep fall to the 8-ring, where the rate equals that of aliphatic ketones with a central carbonyl; finally, there is a rise to the level of aliphatic methyl ketones, which is attained by cyclopentadecanone. There are no corresponding variations in the velocities of the reactions of aliphatic ketones with these reagents.

The surprising stability of the higher cycloparaffins has led to a *modification of the strain theory*. The assumption of an arrangement of carbon atoms in one plane has been abandoned and there is good evidence of a multiplanar distribution which permits of almost strainless models for the higher cycloparaffins. These considerations, which are due mainly to *Sachse* (Z. phys. Ch. **10**, 203; **11**, 185; Ber. **23**, 1365) and to *Mohr* (Ber. **55**, 230; J. pr. Ch. **98**, 315; **103**, 316) apply especially to hydroaromatic compounds, where they will be explained (p. 85). They find support in observations such as *W. Huckel's* discovery of two stereo-isomeric decahydro-naphthalenes (p. 161).

The **ease of formation** is greatest for 5-ring and 6-ring compounds, which, in addition, are readily interconvertible by contraction and expansion of the rings (p. 86). The *Wurtz* synthesis succeeds only in the case of the lower members, while the *Wislicenus* reaction yields excellent results with the intermediate members and is fairly successful even with the higher ones.

Ring formation from dicarboxylic acids does not always conform to expectations based on the classical strain theory. The lower members, 5-, 6- and 7-rings, are obtained with the best yield, 40–50 %. Then the yield of ketone formed drops to a minimum, the yield of the C_{10}-compound being as low as 0·2 %. The higher acids give again yields of a few percent. There are remarkable differences between Ca salts and Th salts (id. Helv. **9**, 499):

Acid (Cyclic ketone)	Glutaric (4-ring)	Adipic (5-ring)	Pimelic (6-ring)	Suberic (7-ring)	Azelaic (8-ring)
Ca salt	0	45	40–50	35	5
Th salt	0	15	70	50	20

On the other hand ketone formation by *Ziegler's* method (p. 79) from dicarboxylic dinitriles is satisfactory even with the larger rings.

In this connection mention should be made of the formation and stability of *unsaturated ring systems.* Compounds with one double bond in the ring are known in all main ring systems from cyclopropane upwards to higher and to high-molecular compounds, such as cyclo-octatetrene and civetone. An acetylene linkage is impossible, however, on account of strain, in any ring with 6 atoms or less. The 7-ring is the first to yield an acetylene derivative, viz. cycloheptine. With still larger rings the triple bond has been successfully introduced by the usual reaction of alcoholic KOH on the dibromides. Cyclopentadecine and cycloheptadecine have been prepared by this method (*Ruzicka* et al., Helv. **16**, 498).

Ruzicka has attempted to show graphically how the actual ease of ring formation found experimentally corresponds with the tendency to ring closure deduced from the distance between the carbon atoms involved and the ring strain (id. Helv. **9**, 499).

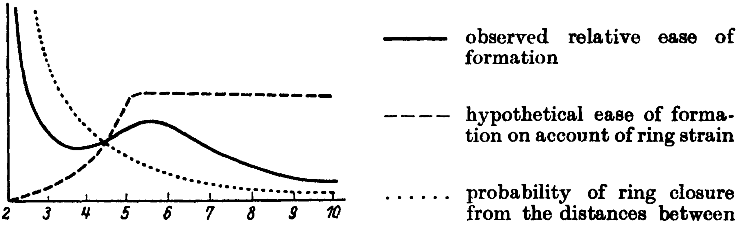
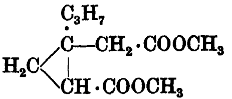


Fig. 1

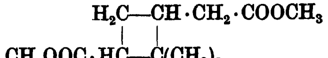
The influence of *substitution* on the stability of ring systems is indicated, e.g., by the fact that cyclohexyl iodide is reduced by HI and P to methylcyclopentane, though cyclohexane itself is completely unaffected. While cyclopropane-1,2-dicarboxylic acid resists conc. HCl (*Buchner,* Ber. **23**, 703; Ann. **284**, 218), caronic acid is readily split to terebic acid (*Baeyer,* Ber. **29**, 2799). A third example is the fact that a methyl group or double bond in the α-position hinders ring closure in dicarboxylic acids (*Ruzicka,* Helv. **11**, 686; **15**, 1459). *Ingold* and *Thorpe* have discussed this matter in their *modified strain theory* in connection with spirocyclic systems (J. **123**, 1172).

Summing up, it can be stated that neither the ease of ring fission, nor the tendency to ring formation permit of any direct conclusions as to the influence of strain. Ring opening is affected by steric factors, substituents, etc., while the closure is influenced by the reactivity of the reactants, by the stability of the products under the conditions of formation, most of all by the probability of the chain ends meeting each other, and finally by the character of the reaction (cf. ring transitions, p. 11).

Apart from the investigation of equilibrium between isomers, a method of very restricted application, and from the measurement of heats of reaction, which offers difficulties, the only reliable way of estimating ring strain consists in measuring the energy content by the **heat of combustion** (*Eisenlohr, Hückel, Roth, Ruzicka, Stohmann, Verkade,* and others). As an example, we will compare the heat of combustion of two pairs of isomeric esters:



1452 kcal.



1441 kcal.

Dimethyl ester $C_9H_{14}O_4$ with a 4-ring 1136·9 kcal
Dimethyl ester $C_9H_{14}O_4$ with a 5-ring 1117·7 kcal

A more direct comparison of ring systems is provided by determining the heats of combustion of the cycloparaffins and dividing them by the number of methylene groups (*Diels*, Ber. **53**, 1277; *Ruzicka*, Helv. **16**, 162):

Ring system	2	3	4	5	6	7	8	15	17	30
Heat of combustion per CH_2	170	168·5	165·5	159	158	158	157·8	157	157·2	156·7

These results are in good accord with chemical evidence derived from the reactions of the different ring systems. In cases other than those of simpler monocyclic compounds, however, the heat of combustion has so far failed to give a clear indication of the conditions of ring strain.

The ratio of the first to the second **dissociation constant** of polymethylene-1,1-dicarboxylic acids is a function of the spacing of the carboxyls and therefore yields some indication as to the directions of the valencies which are not engaged in ring closure (*Vorländer,* Z. phys. Ch. **106**, 220; *Gane, Ingold,* J. **1926**, 10):

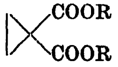
Acid	K_1	K_2
Malonic acid	$6{\cdot}6{\cdot}10^{-3}$	$2{\cdot}0{\cdot}10^{-6}$
Dimethyl-malonic acid	$7{\cdot}7{\cdot}10^{-4}$	$3{\cdot}0{\cdot}10^{-7}$
Cyclobutane-1,1-dicarboxylic acid	$7{\cdot}7{\cdot}10^{-4}$	$3{\cdot}0{\cdot}10^{-7}$
Cyclopropane-1,1-dicarboxylic acid	$2{\cdot}10^{-2}$	$1{,}2{\cdot}10^{-7}$

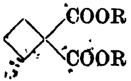
While the constants of cyclobutane-dicarboxylic acid are practically the same as those of an alkylated malonic acid, the values found for the corresponding cyclopropane derivative indicate a marked deflection of carboxyls from their normal positions.

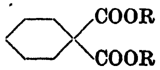
Further, the **electric moments** of cyclic 1,1-dicarboxylic esters (*Farmer,* J. **1933,** 1304) indicate valency deflections of substituents in the different ring systems:

Ring system	3	4	5	6
Electric moment in e.s.u.	$2{\cdot}4{\cdot}10^{-18}$	$2{\cdot}22{\cdot}10^{-18}$	$2{\cdot}14{\cdot}10^{-18}$	$2{\cdot}23{\cdot}10^{-18}$

The **rate of hydrolysis** of cyclic malonic esters has been found by *Gane* and *Ingold* (J. **1926,** 10) to decrease in the following order:







this suggests a maximum distance between the two carboxyl groups in the 3-ring.

The idea of *cis- and trans isomerism* of disubstituted compounds has a precise significance with the small uniplanar rings: the double bond, the 3-, 4- and 5-rings. When applied to higher ring systems, the difference becomes vague, because these rings of 7 or more carbon atoms are not uniplanar. Cf. *Boeseken's* experiments about the relative ease of formation of acetone-glycol compounds in various ring systems, and the related increase of conductivity of their compounds with boric acid (Ber. **46**, 2612; **55**, 3758; **56**, 2411; see also *Windaus*, ib. **56**, 91), the ease of transformation of cis- and trans-forms of 1,2-dicarboxylic acids (*Perkin*, J. **65**, 588; *Alder*, Ann. **504**, 223), and the failure of trans dicarboxylic acids of the 3-, 4- and 5-rings to form anhydrides (*Diels*, Ann. **478**, 142).

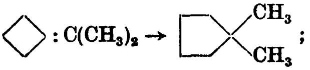
For the physical differences between cis and trans isomers, the rule of *Auwers* and *Skita*, and their methods of formation, see the introduction to the hydroaromatic compounds p. 82 and the description of decalin in the section on polynuclear alicyclic compounds p. 171.

RING TRANSITIONS[1]

After the discussion of ring stability and ring formation in the light of the classical strain theory and of the theory modified to fit modern experimental results, we turn to the related subject of ring transitions, where we find those theories confirmed in the main, though there is an apparent contradiction in some cases. Methods of enlarging and of reducing rings, preceded in every case by an intermediate stage of ring fission, will be considered together. The best known reactions of this kind are the following:

Cyclohexane under the conditions of the *Friedel-Crafts* reaction undergoes isomerisation partly to 1,2-dimethyl-cyclobutane and partly to methyl-cyclopentane (*Ipatiev*, Ber. **44**, 2982; *Zelinsky*, ib. **65**, 1171; *Nenitzescu*, ib. **66**, 1097; id., Ann. **491**, 189).

Reduction by HI and P often results in ring contraction or enlargement. Thus isopropylidene-cyclobutane is hydrogenated to 1,1-dimethyl-cyclopentane (*Schmidt*, Ber. **45**, 1779), while cyclohexyl-cyclohexanol is reduced to cyclohexyl-methyl-cyclopentane (*Nenitzescu*, Ber. **65**, 807)



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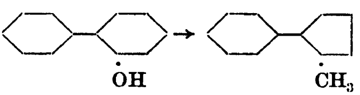

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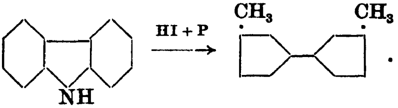
Cyclohexyl and cycloheptyl iodides react similarly with ring contraction to form methyl-cyclopentane and methyl-cyclohexane respectively (*Markovnikov*, J. pr. **49**, 409; Ann. **302**, 36; *Wreden*, Ann. **187**, 163; *Kishner*, J. pr. **56**, 364).

A remarkable transformation is that of carbazole into 3,3′-dimethyl-dicyclopentyl (*Schmidt*, Ber. **45**, 1779)



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One of the earliest observations in this field relates to the **deamination** of cyclic methylamines, systematically investigated by *Demjanov* and by *Wallach*. In addition to normal carbinols (I), cyclanols (II) are formed by ring enlargement, while the higher members yield mainly olefins (*Ruzicka*, Helv. **9**, 399). The reaction can be represented diagrammatically as follows (*Demjanov*, C. 1903 I 828; 1904 I 1214; Ber. **40**, 4393; *Wallach*, Ann. **353**, 321), though there is no evidence for this particular mechanism.

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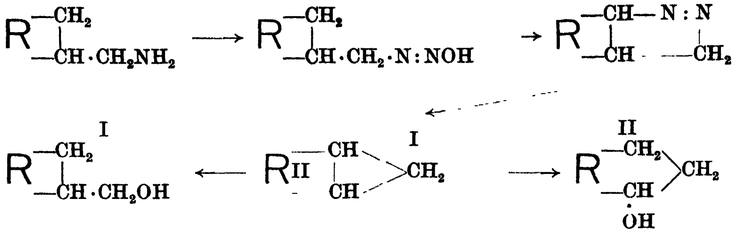
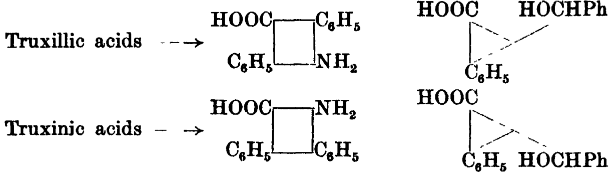
[1] *Nametkin*, Die Umlagerung alicyclischer Kerne. Stuttgart 1926.

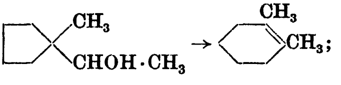


W. Hückel (Theor. Grundlagen der Org. Chem. 2. Aufl. I, 264) assumes a primary formation of a diazonium salt under the influence of acid; the complex kation of the salt, by loss of N_2, gives ions which are transformed into the reaction products by a rearrangement similar to the *Meerwein* transformation (cf. Terpenes).

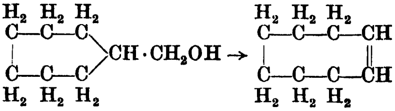
An isolated example of ring contraction under these conditions is afforded by the transformation of truxillic and truxinic acids (p. 41) into phenyl-benzoxyl-cyclopropane-carboxylic acid (*Stoermer*, Ber. **60**, 2566; *Asbrand*, ib. **64**, 2785; *Schenck*, J. pr. **134**, 230):

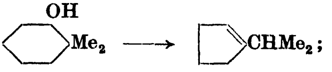


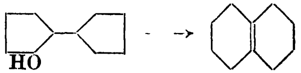
Removal of water from cyclanols (retro-pinacolin transformation) by treatment with oxalic acid or with $ZnCl_2$ may lead to ring transformation, as the following examples show:



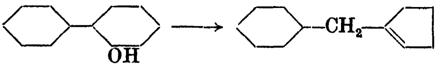
(*Meerwein*, Ann. **417**, 264)





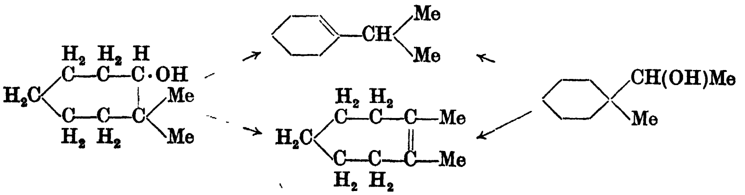


(*W. Huckel*, Ann. **474**, 121; **477**, 131)



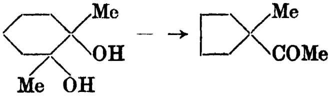
(*W. Huckel*, Ann. **477**, 106)

The characteristic changes which occur with dimethyl-cycloheptanol and with methyl-cyclohexyl-ethanol (*Meerwein*, J. pr. **104**, 289; cf. p. 71) should also be noted:

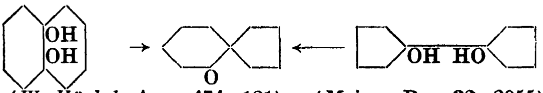


Similarly, the ***elimination of hydrogen halide*** from cyclic compounds is sometimes accompanied by ring transformation, as in the formation of eucarvone from carvone hydrobromide (*Wallach*, Ann. **339**, 94; *Clarke*, J. **97**, 11; cf. p. 249).

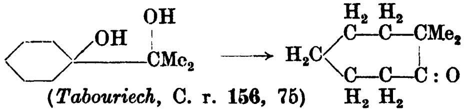
Pinacolin formation from cyclic glycols and *isomerisation* of *cyclic ethylene oxides* may also be accompanied by changes in the ring:



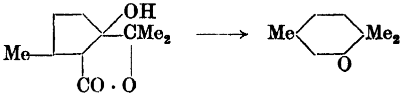
(*Nametkin*, Ber. **57**, 583)



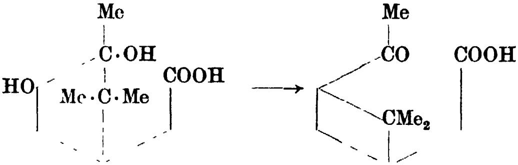
(*W. Hückel*, Ann. **474**, 121) (*Meiser*, Ber. **32**, 2055)



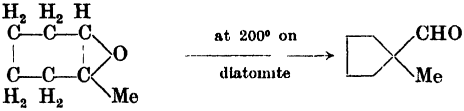
(*Tabouriech*, C. r. **156**, 75)



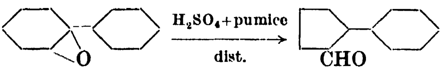
(*Wallach*, Ann. **329**, 83; *Meerwein*, ib. **376**, 154)



(*Tiemann*, Ber. **29**, 3014)



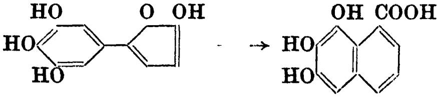
(*Tiffeneau*, C. r. **195**, 1284)

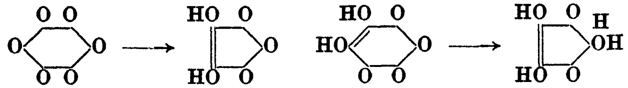


(*Lévy*, C. r. **187**, 45)

The action of $AgNO_3$ on cyclic *iodohydrins* takes a similar course (*Nenitzescu*, Ber. **65**, 807; *Tiffeneau*, C. r. **195**, 1284; *Le Brazidec*, C. r. **159**, 774).

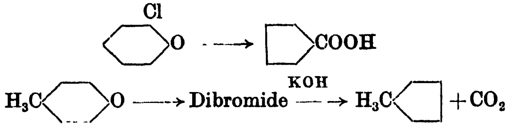
The *benzilic acid transformation* of certain 1,2-diketones under the action of alkalies is a further interesting example. Thus purpurogallin changes to purpurogallone, triquinoyl to croconic acid, rhodizoic acid to croconic acid hydride:



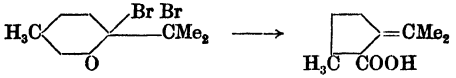


Humulone and lupulone react in a similar way, see p. 400, 401.

α-Halogenated cyclohexanones undergo, in an alkaline medium, an analogous ring contraction which results in the formation of cyclopentanecarboxylic acids or of decarboxylated products derived from them (cf. p. 59).

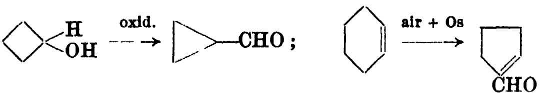


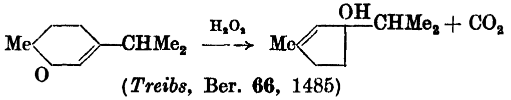
(*Wallach*, Ann. 414, 296)



(*Wallach*, Ann. 327, 149; 329, 108; 414, 233)

Among *oxidations* accompanied by changes of ring structure the following are of special interest:

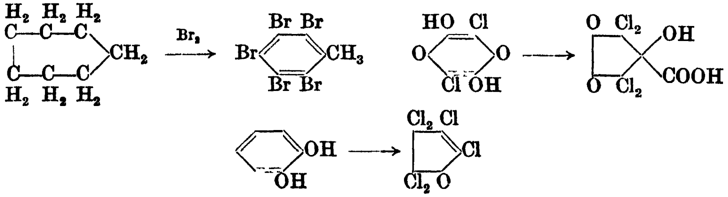




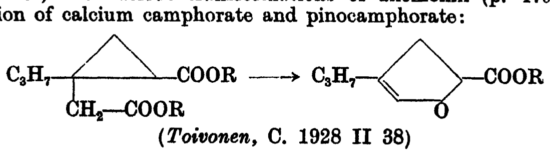
(*Treibs*, Ber. 66, 1485)

Cf. the formation of purpurogallin from pyrogallol by air in an alkaline medium. Oxidation of methylene-cyclobutane with HOCl and PbO leads to ring enlargement and formation of cyclopentanone (*Demjanov*, Ber. 55, 2730).

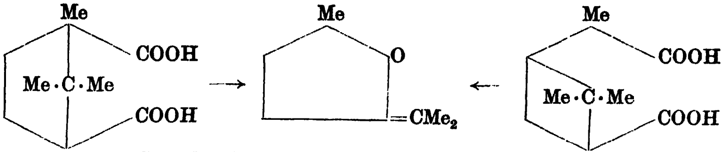
Prolonged *halogenation* of cyclic compounds can also give rise to a transition into a more favoured ring system:



A few special reactions involving *intramolecular ring closure* remain to be mentioned: the internal condensation of isopropyl-cyclopropane-carboxylic acetic ester, the various transformations of anemonin (p. 479) and the distillation of calcium camphorate and pinocamphorate:

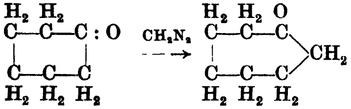


(*Toivonen*, C. 1928 II 38)

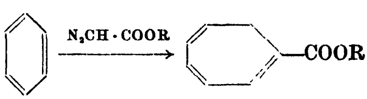


(*Semmler*, Ber. **25**, 3520; *Ruzicka*, Helv. **4**, 666)

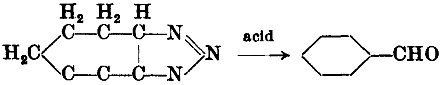
A number of *condensations* of different kinds are known which result in extension or contraction of rings, such as reactions with diazo compounds or phenyl azide,



(*Edwards*, *Reid*, Am. **52**, 3235)

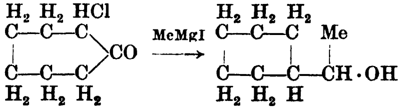


(*Braren* and *Buchner*, Ber. **33**, 684)

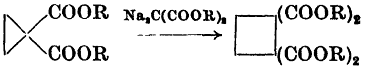


H_2 H_2 H Ph (*Alder*, *Stein*, Ann. **501**, 1)

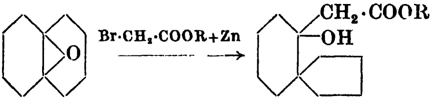
and also *Grignard* reactions, malonic ester condensations and *Reformatzky* syntheses, e.g.:



(*Godchot*, C. r. **186**, 375, 955; *Vavon*, ib. 702)

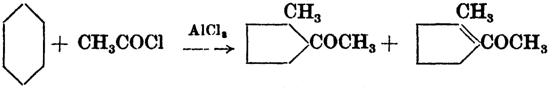


(*Bone*, *Perkin*, J. **67**, 108)



(*Clemo*, *Reid*, Am. **52**, 3235)

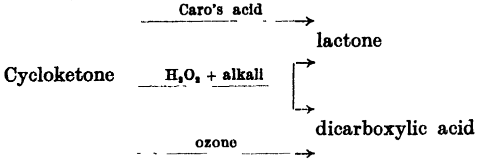
and *Friedel-Crafts* reactions with acyl chlorides, e.g.:



(*Unger*, Ber. **65**, 467; *Hopf*, ib. 482)

A few general reactions will be mentioned, though they are not immediately connected with the ring strain problem. Various cycloparaffins undergo *isomerisation* on heating and give the corresponding unsaturated aliphatic compounds, as cyclopropane → propylene (*Tanatar*, Ber. **29**, 1297), cyclobutane → erythrene etc. In other cases *polymerisation* to high boiling or solid condensation products takes place, as e.g. of 1,1,2-trimethyl-cyclopropane, 1,2-dimethylene-cyclobutane, cyclo-octatetrene. Other ring systems suffer *depolymerisation* into olefinic fragments when exposed to heat or to short wave radiation. Thus truxillic and truxinic acids are reconverted into cinnamic acid. Substituted cyclobutane-1,3-diones are decomposed into the corresponding ketens; caoutchouc, dipentene, etc. give isoprene, etc. The thermal decomposition of benzene to three molecules of acetylene is analogous.

Cycloparaffins are converted by oxidation with SeO_2, by H_2O_2, by CrO_3 or by catalytic autoxidation mainly into α, β-unsaturated ketones (pinene → verbenone, nopinene → pinocarvone (*Dupont*, Bull. **53** (1933), 599; *Treibs*, Ber. **61**, 459). Oxidative decomposition of cyclic ring ketones results in a lactone or a dicarboxylic acid according to the reagent (*Ruzicka*, Helv. **11**, 1159; *Stoll*, ib. **13**, 142):



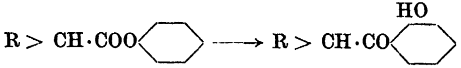
Autoxidation of cyclic α, β-unsaturated ketones (methyl-cyclohexenone, carvone, pulegone, eucarvone etc.) in alkaline alcoholic solution has been found to proceed as follows: the first step is the addition of molecular oxygen, then hydrogen peroxide is set free which oxidises the unchanged ketone to a keto-oxido compound. The latter, in the presence of alcohol, is converted into 1,3-keto-enol or its ether. The intermediate oxide can be isolated if H_2O_2 itself is used, and on treatment with hot alcoholic KOH yields the same keto-ether (*Treibs*, Ber. **66**, 1483 etc.).

The following methods have been worked out for ascertaining the *constitution of cyclic carboxylic acids*, and especially the place of attachment of the carboxyl groups to the ring:

1. *v. Braun's* imido-chloride method (*v. Braun*, Ann. **453**, 113) is based on the different behaviour of acyl amides towards PCl_5:

$$\begin{array}{rcl} R\cdot CH_2\cdot CONHEt & \longrightarrow & R\cdot CCl_2CONHEt \\ R_2:CH\cdot CONHEt & \longrightarrow & R_2:CCl\cdot CONHEt \\ R_3\vdots C\cdot CONHEt & & \text{unchanged} \end{array}$$

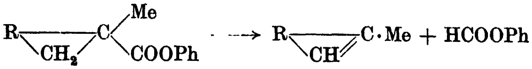
2. Superheating of the carboxylic phenyl esters of the alicyclic series (*Skraup*, Ber. **62**, 1127) results in o-hydroxy-phenyl ketones, if the carboxyl is attached to the ring,



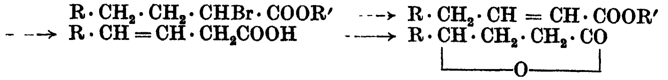
while cyclane-acetic acids, e.g. trimethyl-cyclopentane-acetic acid, split off CO_2 and give the corresponding hydrocarbon, e.g. trimethyl-benzyl-cyclopentane:

$$R > CH\cdot CH_2\cdot COOPh \longrightarrow R > CH\cdot CH_2\cdot Ph + CO_2$$

1-Alkyl-cycloparaffin-1-carboxylic acids yield 1-alkyl-Δ^1-cyclo-olefins together with phenyl formate:



3. Cyclic α-bromo-aliphatic esters are converted into α, β-cyclo-olefinic acids which through the intermediate stage of β, γ-unsaturated acids isomerise to γ-lactones:



$$\begin{array}{lcl} R\cdot CH_2\cdot CH_2\cdot CHBr\cdot COOR' & \longrightarrow & R\cdot CH_2\cdot CH = CH\cdot COOR' \\ \longrightarrow R\cdot CH = CH\cdot CH_2COOH & \longrightarrow & R\cdot CH\cdot CH_2\cdot CH_2\cdot CO \\ & & \quad\underbrace{\qquad\qquad\qquad}_{O} \end{array}$$

4. The acid is converted into an olefin either (method I) by way of the methylamine, or (method II) by way of the amine (*Hofmann* degradation),

and exhaustive methylation. The olefins are oxidised to carboxylic acids. The acid resulting from method I has one carbon less than the original acid, while method II results in an acid containing two carbon atoms less (*Willstätter*, Ann. **472**, 121; *v. Braun*, *ib.* **490**, 109):

$$\text{I.}\quad \mathrm{R\cdot CH_2\cdot COOH} \xrightarrow{\text{Na + alcohol}} \mathrm{R\cdot CH_2\cdot CH_2OH} \xrightarrow[\mathrm{NH_3}]{\text{bromide}} \mathrm{R\cdot CH_2\cdot CH_2NH_2}$$

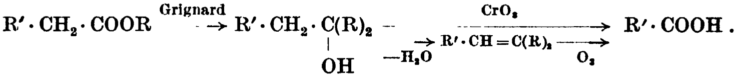
$$\xrightarrow[\text{distillation}]{\text{methylation}} \mathrm{R\cdot CH{=}CH_2} \xrightarrow{\mathrm{O_3}} \mathrm{R\cdot COOH},$$

$$\text{II.}\quad \mathrm{R'\cdot CH_2\cdot CH_2\cdot COOH} \xrightarrow[\mathrm{NH_3}]{\text{chloride}} \mathrm{R'\cdot CH_2\cdot CH_2\cdot CONH_2}$$

$$\xrightarrow[\text{degradation}]{\text{Hofmann}} \mathrm{R'\cdot CH_2\cdot CH_2\cdot NH_2} \xrightarrow[\text{distillation}]{\text{methylation}} \mathrm{R'\cdot CH{=}CH_2} \xrightarrow{\mathrm{O_3}} \mathrm{R'\cdot COOH}.$$

Acids which have the carboxyl attached to the ring are converted by method I into cyclic ketones. Homologous acids do not give cyclic ketones until the operation I or II has been repeated the necessary number of times. Cf. the application to naphthenic acids p. 65.

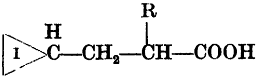
5. *Wieland's* degradation method has been successfully applied to the bile acids (p. 552, *Wieland*, Z. physiol. Ch. **161**, 80; cf. *Tschesche*, Ann. **498**, 185; *Chuang*, ib. **500**, 270). The carbinol obtained by means of MeMgI or PhMgBr is converted into a carboxylic acid according to the scheme:

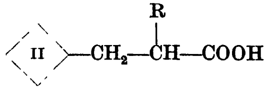


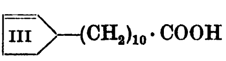
$$\mathrm{R'\cdot CH_2\cdot COOR} \xrightarrow{\text{Grignard}} \mathrm{R'\cdot CH_2\cdot \underset{\displaystyle OH}{\underset{|}{C}}(R)_2} \xrightarrow{\mathrm{CrO_3}} \mathrm{R'\cdot COOH}.$$
$$\xrightarrow{-\mathrm{H_2O}} \mathrm{R'\cdot CH{=}C(R)_2} \xrightarrow{\mathrm{O_3}}$$

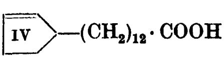
While reactions 1 and 2 give information only about the carbon in the α-position and indicate a primary, secondary or tertiary linkage of the carboxyl group, degradation according to 3, 4 or 5 makes it possible to determine the complete structure of the side chain to which the carboxyl is attached.

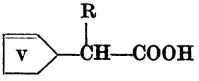
Carboxylic acids of the lower ring systems, containing altogether 15 to 19 carbon atoms, are pharmacologically important, e.g. cyclopropane and cyclobutane fatty acids of types (I) and (II), the pentacarbocyclic hydnocarpic acid (III) and chaulmoogric acid (IV) and the synthetical acids (V) and (VI), and cyclohexane carboxylic acids with long side chains (VII). For their action on *Mycobact. leprae*, the bacterium causing leprosy, cf. *Adams*, Am. **49**, 2934; **50**, 1475; **54**, 1548 etc.; *Walker*, Bull. chim. pharm. **66** (1927), 610.

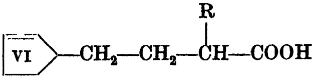


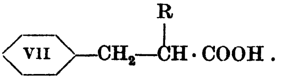










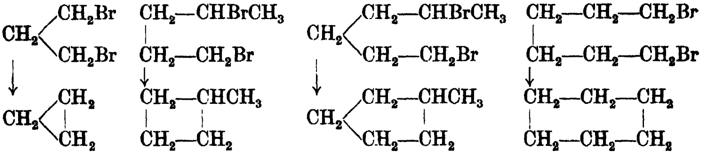


The odour of the ketones varies with the number of ring-members. Methylamylenyl-cyclopentenone smells of jasmine, intermediate members up to C_{12} have a smell reminiscent of camphor, cyclotridecanone that of cedar wood. The higher ketones C_{14} to C_{18} are characterised by a smell like that of musk. It is worth noticing that the related alcohols do not possess this odour (*Ruzicka*, Helv. **18**, 1152).

METHODS OF RING FORMATION IN CYCLOPARAFFIN DERIVATIVES

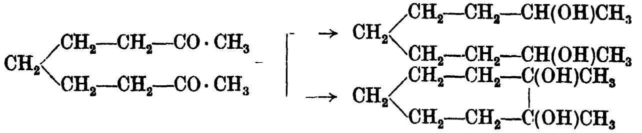
The methods which can be used for converting open carbon chains into closed rings do not differ in principle from those used for linking two carbon chains together, the only distinction being that the two atoms which are to be linked are already united through other carbon atoms. Hence many of the condensation reactions of aliphatic chemistry can be used under the appropriate conditions for the synthesis of the cycloparaffins and their derivatives. The more important reactions of this kind can be summarised as follows.

(1a) The cycloparaffins themselves are formed by the action of sodium (*Wurtz'* reaction, see I, 96 under paraffins), or of zinc (*Ullmann*, Ber. **20**, R. 706; *Lespieau*, Bull. **47** (1930), 847) on dibromo-paraffins (the hydrobromic esters of glycols):

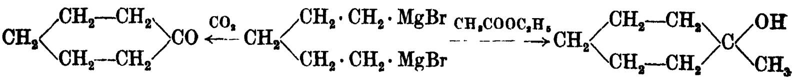


(1b) Cyclopropane, cyclobutane and cyclopentane derivatives can be obtained by treating γ-, δ- and ε-bromo derivatives of ketones, aliphatic esters or nitriles with alcoholic potash, quicklime etc. (*Blanc*, C. r. **145**, 78; *Kishner*, C. 1909 II 1130).

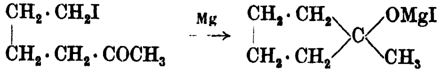
(2) *Intramolecular pinacol formation.* In the reduction of ketones secondary alcohols are formed together with di-tertiary glycols termed "pinacols". The reduction of diacetyl-pentane gives an aliphatic di-secondary glycol, and also a di-tertiary glycol or cyclic pinacol: (*Kuhn*, C. 1898 I 888; *J. Wislicenus*, Ann. **302**, 91):



(3a) *Ring syntheses by means of metallo-organic compounds.* If the dimagnesium compound of 1,5-dibromo-pentane is treated with ethyl acetate, methyl-cyclohexanol is formed. Carbon dioxide reacts to give cyclohexanone:

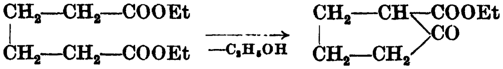


The synthesis of a tertiary alcohol from magnesium-alkyl iodide and a ketone (I, 133) takes place intramolecularly when magnesium reacts with δ-acetobutyl iodide:



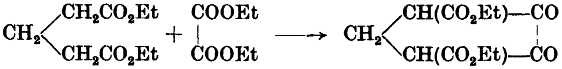
3b. *Paraffins* are partially converted by *dehydrogenation* at the boiling point in presence of $AlCl_3$ into monocyclic and dicyclic paraffins. In this reaction isomerisation, condensation to higher aliphatic compounds and chain fission go on side by side (*Nenitzescu*, Ber. **66**, 1892).

4a. *Intramolecular ester condensation.* When sodium reacts with adipic ester, a condensation similar to the formation of aceto-acetic ester takes place within the molecule and a cyclic β-keto ester is formed (*Dieckmann*):



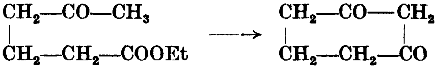
Dialkyl-acetone-dicarboxylic esters undergo an analogous ring closure to give cyclobutane derivatives (*Schroeter*). In a similar way pimelic esters give β-keto esters with a six-membered ring.

4b. *Oxalacetic ester condensation.* Oxalic ester and glutaric ester with sodium ethoxide as condensing agent combine to give cyclopentanedione-dicarboxylic ester:



β-Substituted glutaric esters, acetone-dicarboxylic esters, methylethyl ketone, dibenzyl ketone etc. undergo analogous condensations with oxalic ester in the presence of NaOEt.

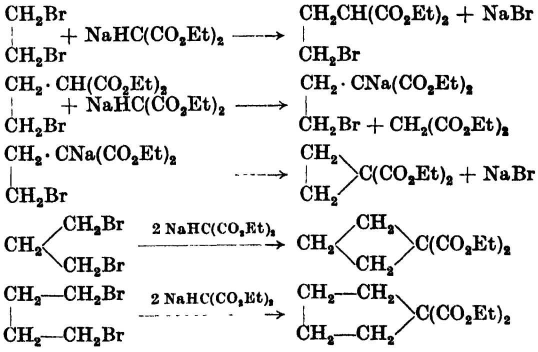
4c. *Intramolecular formation of β-diketones.* γ-Acetyl-butyric ester is converted into 1,3-cyclohexanedione by the action of sodium ethoxide:



With ε- and ζ-keto-esters the reaction results in the formation of extracyclic β-diketones of the cyclopentane and cyclohexane series.

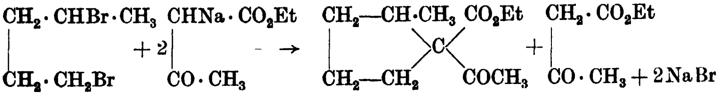
4d. Intramolecular *condensation of ε- and η-keto-esters,* analogous to the *Perkin* reaction, takes place on thermal decomposition, resulting in 5- and 6-ring derivatives (e.g. 12-ketocholanic acid, *Lettré,* Z. physiol. Ch. **218,** 67).

5. *Cyclic syntheses with malonic, aceto-acetic and analogous esters.* This method is due to *W. H. Perkin* jun. (see J. **1929.** 1347). Sodiomalonic ester combines with alkylene dibromides to cycloparaffin-carboxylic esters, by a three-stage reaction:



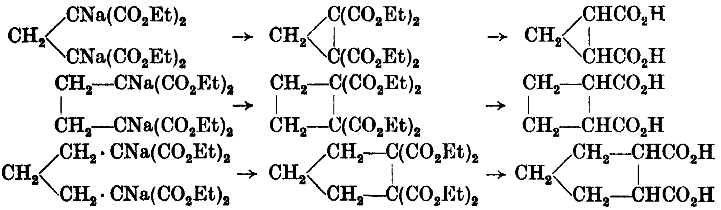
Instead of alkylene bromides the bromine addition products of olefin-monocarboxylic and olefin-dicarboxylic esters, and also of unsaturated ketones, may be used, and the reaction has thus served for preparing numerous cyclopropane derivatives. Cyano-acetic ester behaves similarly to malonic ester (*Carpenter, Perkin,* J. **75**, 921; *Kohler,* Am. **39**, 1404, 2405).

By the action of sodio-aceto-acetic ester on 1,4-dibromo-pentane, 1-methyl-2-acetyl-cyclopentane-2-carboxylic ester is formed (*Colman, Perkin,* Ber. **21**, 742):



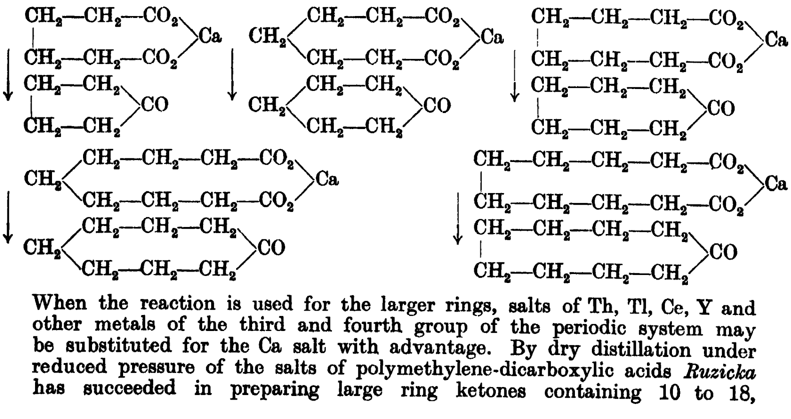
In a similar way α-acetyl-cyclohexane-carboxylic ester is obtained from 1,5-dibromo-pentane (*v. Braun,* Ber. **40**, 3943). The synthesis of suberone-dicarboxylic ester from 1,4-dibromo-butane and acetone-dicarboxylic ester (id. Ber. **46**, 1792) belongs to this same class of ring syntheses from halogen derivatives and compounds containing reactive methylene groups.

6. Sodium is removed from the di-sodium compounds of alkylene-dimalonic esters by iodine or bromine and ring closure follows, resulting in the formation of cycloparaffin-tetracarboxylic acids. By elimination of $2CO_2$, cycloparaffin-dicarboxylic acids are then obtained (*W. H. Perkin* jun.). The reaction is analogous to the formation of diacetyl-succinic ester from iodine and sodio-aceto-acetic ester or of ethane-tetracarboxylic ester from iodine and sodio-malonic ester:



The di-sodium compound of α, α′-diacetyl-adipic ester behaves similarly towards iodine.

7a. *Cyclic ketone formation.* Just as calcium salts of paraffin mono-carboxylic acids furnish open-chain ketones by distillation, so some calcium salts of higher normal paraffin dicarboxylic acids give cyclic ketones on dry distillation (*J. Wislicenus*):

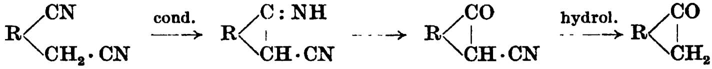


When the reaction is used for the larger rings, salts of Th, Tl, Ce, Y and other metals of the third and fourth group of the periodic system may be substituted for the Ca salt with advantage. By dry distillation under reduced pressure of the salts of polymethylene-dicarboxylic acids *Ruzicka* has succeeded in preparing large ring ketones containing 10 to 18, and even 30 and 32 carbon atoms. (Cf. introduction and polycarbocyclic compounds.)

Methyl groups and double bonds in the α-position to the carboxyl group prevent ring closure (*Ruzicka*, Helv. **11**, 686; **15**, 1459).

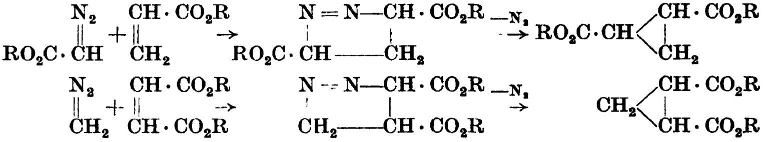
7b. Adipic and pimelic anhydrides and their alkyl substitution products dissociate, on distillation at ordinary pressure, into CO_2 and cyclic ketones (*Blanc*, cf. I, 561). For the application of this reaction to the determination of ring size in cyclic compounds see *Blanc*, C. r. **144**, 1356; *Windaus*, Z. physiol. Ch. **130**, 116; *Stange*, ib. **218**, 74 etc.

8. *Dinitriles*, when condensed with the aid of phenyl-ethyl-lithium-amide, give cyano-cycloketones, which are hydrolysed to the corresponding cyclanones (*Ziegler*, Ann. **504**, 94):



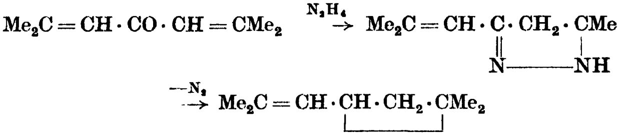
This method is particularly valuable for the synthesis of large ring ketones, which cannot be prepared, or only with very low yields, by heating the salts of dicarboxylic acids.

9a. *Aliphatic diazo compounds*, such as diazomethane (I, 251) and diazo-acetic ester, combine additively with olefin-monocarboxylic and olefin-dicarboxylic esters to give cyclic azo compounds or pyrazoline derivatives, which readily split off nitrogen and yield cyclopropane-carboxylic acids (*Buchner*):

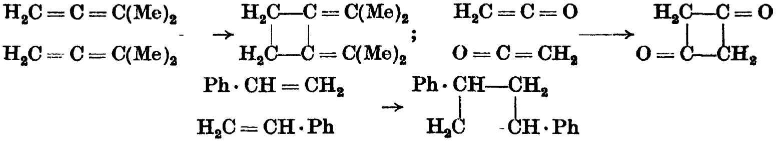


Cf. the condensation of benzene with diazo-acetic ester to pseudophenyl-acetic or norcaradiene-carboxylic ester.

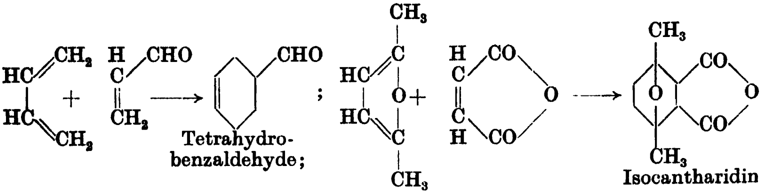
9b. *Unsaturated aldehydes and ketones*, like isobutylidene aldehyde, phorone, (di-)benzylidene-acetone and others combine with hydrazine to pyrazolines, which are readily converted, by elimination of nitrogen, into cyclopropane derivatives (*Kishner*, C. 1913 II 2133; 1916 II 318; 1923 III 669):

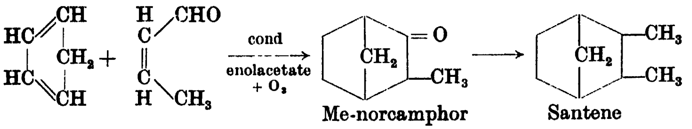


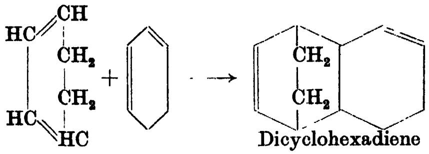
10a. *Dimerisation of allene, keten, styrene* and their derivatives leads to the cyclobutane series, e.g.:



10b. *The Diels-Alder diene synthesis*, a reaction of wide application, is important for synthesising natural hydroaromaticcompounds derived from cyclohexane, and also the derivatives of endo-alkylene cyclohexanes. The principle of the reaction is the condensation of a compound containing conjugated double bonds with a second unsaturated reactant:







Cf. hydroaromatic compounds p. 86, condensed rings p. 161, bridged rings p. 181. See *Alder*, Ann. **514**, 1, 197; *Wassermann*, J. **1935**, 1511 for the stereochemistry of diene syntheses.

Ia. MONONUCLEAR TRI-, TETRA-, PENTA-, HEPTA-, OCTA- AND POLYCARBOCYCLIC COMPOUNDS

1. CYCLOPROPANE GROUP

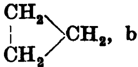
Cyclopropane derivatives are of infrequent occurrence in nature. The pyrethrins are esters of pyrethrolone and chrysanthemic acids, which belong to the cyclopropane series. In some bicyclic natural products, e.g. sabinol, carene, thujone (p. 239), a 3-ring forms part of the molecule, and cyclopropane-carboxylic acids, such as α-tanacetonic and caronic acid, are among their oxidation products.

In general, synthetical methods must be used for obtaining cyclopropane derivatives. In addition to the general methods of ring closure, such as the action of Na or Zn on 1,3-dibromides (*Wurtz*), of ethylene dibromide on sodio-malonic ester (*Perkin*), of I_2 on disodio-alkylene-dimalonic esters, and of alkali on γ-halogenated fatty acids, there are two special modes of formation available:

the condensation of olefins with aliphatic diazo compounds, and
the reaction of α, β-unsaturated aldehydes or ketones with hydrazine.

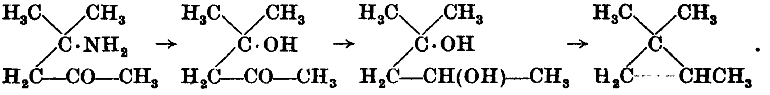
The physical properties, the ease of formation and stability, the fission and enlargement, of the 3-ring, have been discussed in the introductory remarks on cycloparaffins, above. The stereochemistry of the cyclopropane series has been elucidated by researches into the isomerism of the carboxylic acids, viz. phenyl-benzoyl-cyclopropane-carboxylic acids, methyl-cyclopropane-dicarboxylic acids etc.

HYDROCARBONS

Cyclopropane, *trimethylene*  b.p. –33°, is a readily condensable gas, and a narcotic. It has been prepared from trimethylene bromide and sodium (*Freund* 1882), or with alcohol and zinc dust or zinc wool with exclusion of moisture (*Ullmann*, Ber. **20**, R. 706; *Gustavson*, J. pr. **76**, 512; *Godchot*, C. r. **202**, 1629; *Ashdown*, Am. **58**, 850). It combines with Br_2, especially when HBr is present, though less readily than propylene, forming mainly trimethylene bromide $CH_2Br \cdot CH_2 \cdot CH_2Br$ (*Gustavson*, C. r. **131**, 273); with HI, it forms *n*-propyl iodide. At a dull red heat it is converted into propylene (*Tanatar*, Ber. **32**, 1965); the kinetics of this transformation have been studied by *Trautz* (J. pr. **104**, 53). A method of estimating propylene and cyclopropane side by side with the aid of BrI-solution has been worked out by *Roginsky* (Am. **55**, 1800). H_2, in the presence of finely divided Ni, reduces it to propane even at 80° (*Willstätter*, Ber. **40**, 4456). $KMnO_4$-solution, at ordinary temperature, does not attack it (*Torno*, Ber. **21**, 1282). *Berthelot* has measured the heat of formation and compared it with that of propylene (C. r. **129**, 483).

Methyl-cyclopropane, b.p. 4° (*Demjanov*, Ber. **28**, 22; C. 1902 I 1277).

1,2-Dimethyl-cyclopropane C_5H_{10}, two stereoisomers, cis, b.p. 28·8–29°, d_{20} 0·6769, and trans, b.p. 37·2–37·4°, d_{20} 0·6928, from 2,4-dibromopentane (*Baudrenghien*, Ac. Belg. **15** (1929), 53), reacts with HNO_3 to give Me_2-isopropyl-alcohol (*Kishner*, C. 1914 I 1496). **Ethyl-cyclopropane** C_5H_{10}, b.p. 36·5–37°, from acetyl-cyclopropane with N_2H_4 (*Philipov*, J. pr. **93**, 162). **1,1,2-Trimethyl-cyclopropane** C_6H_{12}, b.p. 57–59°, has been obtained from diacetone-amine through the glycol and the dibromide by Wurtz' method (*Zelinsky*, Ber. **34**, 2856):



It is also obtained by heating Me_3-pyrazoline (vol. IV) with KOH. It polymerises to a mixture of high-boiling compounds and gives a dibromide b.p. 87–89°/23 mm. (*Kishner*, C. 1912 I 2025). **1,2,3-Trimethyl-cyclopropane** b.p. 65–67° is prepared in the same way as the 1,1,2-compound, through the glycol and the dibromide, from Me-acetyl-acetone $CH_3 \cdot CO \cdot CHMe \cdot CO \cdot CH_3$ (*Zelinsky*, Ber. **34**, 2865).

1-Methyl-2-ethyl-cyclopropane C_6H_{12} b.p. 64–65°, from hexane-diol-2,4, obtained from aldol + EtMgBr; the dibromide of the diol is treated with zinc dust. It decolorises $KMnO_4$-solution (*Lespieau*, C. r. **192**, 1395).

1-Methyl-2-propyl-cyclopropane C_7H_{14} b.p. 92–93° (id. ib. p. 1572).

Vinyl-cyclopropane. The substance formerly described under this name has been found to be a mixture of methyl-cyclobutene and methylene-cyclobutane (*Favorsky*, Ber. **47**, 1648). The true vinyl-cyclopropane C_5H_8, b.p. 40°, smells of garlic. It is prepared from acetyl-cyclopropane (p. 25) through the oxime, which is reduced and exhaustively methylated to Me_3-(α-cyclopropylethyl)-NI; the latter is distilled with Ag_2O. Gentle oxidation with $KMnO_4$ gives cyclopropyl-glycol (see below) (*Demjanov*, Ber. **55**, 2718): hydration produces cyclopropyl-Me-carbinol (p. 24), and catalytic reduction gives Et-cyclopropane (above) (id. C. 1913 I 2027).

1-Methyl-1-cyclopropyl-ethylene C_6H_{10} b.p. 71–71·5° from dimethyl-cyclopropylcarbinol (cf. below) with acetic anhydride (*Kishner*, C. 1911 II 363).

1,1-Dimethyl-2-isobutenyl-cyclopropane C_9H_{16} b.p. 132°, from the pyrazoline obtained from phorone (I, 273) and N_2H_4, with KOH (id. C. 1913 II 2131).

1-Methyl-isohexenyl-cyclopropane $C_{10}H_{18}$, b.p. 160°/735 mm., similarly from citral + N_2H_4 → citral-pyrazoline, which is treated with KOH and platinum black. It gives 1-methyl-1-γ-keto-isohexyl-methane by oxidation with $KMnO_4$ and trimethyl-isohexyl-methane by catalytic reduction (id. C. 1923 III 669).

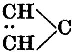
Phenyl-cyclopropane C_9H_{10} m.p. —36°, b.p. 170·5° is obtained from cinnamic aldehyde + N_2H_4, through Ph-pyrazoline, which is treated with KOH (*Kishner*, C. 1913 II 2130), or from cinnamyl bromide + HBr and debromination (*Lespieau*, C. r. **190**, 1129; Bull. **47** (1930), 847). It polymerises with acids. By a similar reaction **1,2-diphenyl-cyclopropane** $C_{15}H_{14}$ has been prepared from benzylidene-acetophenone and hydrazine through 3,5-Ph_2-pyrazoline.

1,1,2,2-Tetraphenylcyclopropane, m.p. 165·5°, is obtained from 1,1,3,3-tetraphenyl-1,3-dimethoxypropane by the successive action of KNa and tetramethyl-ethylene dibromide (*Wittig*, Ber. **67**, 2053).

Monochloro-cyclopropane C_3H_5Cl, b.p. 43°, and **dichloro-cyclopropane** $C_3H_4Cl_2$, b.p. 74°, (*Bruhl*, Ber. **25**, 1954) are formed by the action of chlorine on cyclopropane in daylight (*Gustavson*, J. pr. **42**, 496; **43**, 396). **1,2-Dibromo-cyclopropane** $C_3H_4Br_2$, an oil of sweetish odour, m.p. 0°, b.p. 45°/27 mm., is obtained from cyclopropene (cf. below) and Br_2 and is reconverted into cyclopropene by the action of Zn in EtOH (*Demjanov*, Ber. **56**, 2200). **1,2-Diiodo-cyclopropane** $C_3H_4I_2$ is prepared similarly; it melts below —5° and is unstable (id. C. 1931 I 930).

Amino-cyclopropane $C_3H_5NH_2$ b.p. 49°, from cyclopropane-carboxylic amide with KOBr (*Kishner*, C. 1901 II 579), is miscible with water in all proportions, and smells like propylamine. It is converted into allyl alcohol by nitrous acid, the ring being opened (id. C. 1905 I 1704).

Dimethylamino-cyclopropane $C_3H_5N(CH_3)_2$ b.p. 60°, *picrate* m.p. 191–192°, is obtained together with cyclopropene (cf. below) by heating trimethyl-cyclopropyl-ammonium hydroxide to 300° (*Demjanov*, Ber. **56**, 2200).

Cyclopropene  $\overset{CH\diagdown}{\underset{CH\diagup}{\vdots}}\!>CH_2$, a gas of characteristic odour, burning with a luminous sooty flame, is formed together with allylene (which can be removed by Cu_2Cl_2) when trimethyl-cyclopropyl-ammonium hydroxide is heated to 300° (*Demjanov*, Ber. **56**, 2200).

1-Methyl-Δ¹-cyclopropene, a gas, is obtained from 1,3-dibromo-isobutylene $CH_2Br\cdot C(CH_3):CHBr$, by zinc dust and alcohol, together with a little isobutylene (*Merishovski*, C. 1914 I 2161).

Nitro-cyclopropanes are described by *Kohler*, Am. **41**, 1379; **50**, 884; **52**, 424, 1174; *Darling*, Am. **53**, 1117.

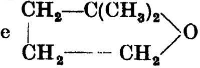
ALCOHOLS

Cyclopropyl carbinol, $C_3H_5CH_2OH$, b.p. 123°, is prepared by reducing cyclopropyl-carboxylic ester with Na and EtOH (*Demjanov*, Ber. **40**, 4397) or from bromo-cyclopropane, trihydroxy-methylene and Mg (*v. Braun*, Ber. **59**, 1081). It yields 1,3-dibromo-butane with conc. HBr (*Demjanov*, C. 1908 I 818). Homologous alkyl-cyclopropyl carbinols cf. *Bruylants*, Belg. **36**, 153.

Cyclopropyl-methyl carbinol $C_3H_5CH(OH)CH_3$ is a colourless viscous oil, b.p. 119–120°, made from acetyl-cyclopropane (cf. below) by reduction with Na and EtOH (*Michiels*, Ac. Belg. **1912**, 16). It forms halides with HCl and HBr, b.p. 105–106° and 118–120° resp. **Cyclopropyl-ethyl carbinol,** b.p. 140°, **Cyclopropyl-isopropyl carbinol,** b.p. 151°, and other homologous compounds (id. Belg. **24**, 396) are obtained by reduction of the corresponding ketones or by the *Grignard* reaction (*Henry*, ib. **40**, 647).

Cyclopropyl-methyl bromide $C_3H_5CH_2Br$ b.p. 58–60°/15 mm. from the carbinol (*v. Braun*, Ber. **59**, 1081). **Cyclopropyl-methyl amine** $C_3H_5CH_2NH_2$

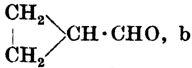
b.p. 86°, prepared from cyclopropyl-carboxylic nitrile by reduction, gives with nitrous acid, by ring enlargement, cyclobutanol, together with cyclopropyl carbinol (*Demjanov*, Ber. **40**, 4393). **β-Cyclopropyl-ethyl amine** $C_3H_5CH_2CH_2NH_2$, *benzoate* m.p. 46–47°, is obtained by reduction of cyclopropyl-acetonitrile (*v. Braun*, Ber. **59**, 1081).

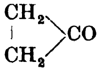
Cyclopropyl-dimethyl carbinol, $C_3H_5C(CH_3)_2OH$, b.p. 127°, is obtained from acetyl-cyclopropane or cyclopropane-carboxylic ester with MeMgl. *Chloride* b.p. 132°, *bromide* b.p. 152°. With oxalic acid the ring opens and dimethyl-tetramethylene oxide  $\begin{matrix}CH_2-C(CH_3)_2\\ |\\ CH_2-CH_2\end{matrix}\!\!>O$ is formed (*Zelinsky*, Ber. **34**, 3887).

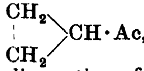
Cyclopropyl-diethyl carbinol, $C_3H_5C(C_2H_5)_2OH$, b.p. 158°; **Cyclopropyl-methyl-ethyl carbinol,** $C_3H_5C(CH_3)(C_2H_5)OH$, b.p. 141° (*Bruylants*, Ac. Belg. **1908**, 1011). Other tertiary alcohols of the type $C_3H_5\cdot C(OH)RR'$, prepared from ketones $C_3H_5\cdot COR$ with alkyl-Mg-halides, have been described (id. Belg. **36**, 153, 519; Ann. Brux. **47**, II, 27).

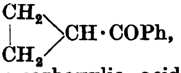
Cyclopropyl glycol $C_3H_5CH(OH)CH_2OH$, b.p. 213–215°, is prepared from vinyl-cyclopropane (cf. above) by the action of $KMnO_4$ (*Demjanov*, Ber. **55**, 2718).

ALDEHYDES AND KETONES

Cyclopropane aldehyde  $\begin{matrix}CH_2\\ |\\ CH_2\end{matrix}\!\!>CH\cdot CHO$, b.p. 98°, is prepared from cyclopropyl carbinol by oxidation with chromic acid.

Cyclopropanone  $\begin{matrix}CH_2\\ |\\ CH_2\end{matrix}\!\!>CO$ is formed from diazomethane and an excess of keten in absolute ether (*Ott*, J. pr. **130**, 177; *Lipp*, Ann. **499**, 23). All attempts to isolate the ketone result in rapid polymerisation. If the ether is evaporated in the presence of moisture the hydrate $C_3H_6O_2$ m.p. 71–72° is formed, which isomerises into propionic acid. Keten and diazo-methane react in dry ether containing methanol to form the methyl-semiacetal, $C_4H_8O_2$, b.p. 45–46°/14 mm. The ethyl-semiacetal isomerises under the influence of aqueous KOH to ethyl propionate b.p. 99°.

Acetyl-cyclopropane,  $\begin{matrix}CH_2\\ |\\ CH_2\end{matrix}\!\!>CH\cdot Ac$, b.p. 113°, can be obtained from aceto-propyl bromide by elimination of HBr with KOH, or by heating acetyl-propane-carboxylic acid, or by the action of MeMgI on cyclopropyl cyanide, or finally from α, β-methyl-cyclopropyl-ethylene by oxidation with $KMnO_4$. With inorganic acids the ring is opened. For homologous ketones see *Bruylants*, Ac. Belg. **1908**, 1011; for homologous ketones with alkyl residues, *Michiels*, Belg. **24**, 396; *Kishner*, C. 1923 III 669; *Wohlgemuth*, Ann. chimie (9) **3**, 141; *Bruylants*, Ann. Bruxelles **47** II 27; Belg. **36**, 519.

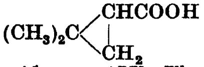
Benzoyl-cyclopropane,  $\begin{matrix}CH_2\\ |\\ CH_2\end{matrix}\!\!>CH\cdot COPh$, m.p. 5°, b.p. 248°, is obtained from benzoyl-cyclopropane-carboxylic acid at 200°, and from γ-chloro-butyrophenone and KCN in abs. MeOH (*Allen*, Can. J. Res. **9**, 159). *Oxime*, m.p. 88°. Homologous ketones with aryl residues: *Haller*, C. r. **154**, 1567; *Kohler*, Am. **41**, 1249, 1379; **50**, 884.

CYCLOPROPANE CARBOXYLIC ACIDS

These compounds are formed by the general methods of ring synthesis given on p. 19, numbers 5 and 6, and by method 9a, which is specific for cyclopropane derivatives (*Buchner*, Ann. **284**, 197). Cyclopropane-polycarboxylic acids in which two carboxyl groups are attached to the same carbon atom can be converted, by loss of CO_2, into carboxylic acids containing one carboxyl less. Interesting cases of cis-trans isomerism, reminiscent of the trithioaldehydes (I, 246), arise from the position of the carboxyls either on the same side or on opposite sides of the plane of the cyclopropane ring.

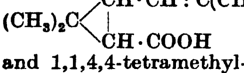
Cyclopropane-carboxylic acid, $C_3H_5CO_2H$, m.p. 18°, b.p. 183° (*Fichter*, Ann. **227**, 24; *Perkin*, J. **47**, 815) is isomeric with crotonic acid. The cyclopropane ring is opened by bromine, α, γ-dibromo-butyric acid being formed (*Kishner*, C. 1909 II 1130). The *nitrile*, b.p. 135°, has been prepared by distilling γ-chloro-butyronitrile from KOH, and by the action of KCN on trimethylene chlorobromide and subsequent ring closure (*Haller*, C. r. **154**, 1567). *Ethyl ester*, b.p. 134°; *chloride*, b.p. 121°; *amide*, m.p. 124° (*Kishner*, C. 1901 II 579; *Dalle*, Ac. Belg. **1902**, 36); *anilide*, m.p. 112°. Chlorine, on heating, converts it into a mixture of α, γ-dichloro-butyric acid and chloro-cyclopropane-carboxylic chloride, b.p. 141—143°; from the latter the free chloro-cyclopropane-carboxylic acid, $C_3H_4ClCOOH$, m.p. 70—71°, can be obtained (*Bruylants*, Ac. Belg. **1921**, 702). On electrolysing equivalent amounts of cyclopropane-carboxylic acid and its potassium salt the allyl ester is formed; the reaction proceeds through cyclopropane-percarboxylic acid, which loses CO_2 and forms allyl alcohol, possibly by way of cyclopropanol (*Fichter*, Helv. **6**, 450). The reaction of the silver salt with iodine results in the triglyceride of cyclopropane-carboxylic acid, $C_{15}H_{20}O_6$, b.p. 144°/0·04 mm., the allyl ester presumably being an intermediate (*Lipp*, Ann. **499**, 1).

2-Methyl-cyclopropane carboxylic acid, b.p. 96·5°/14 mm., is prepared from 1-methyl-cyclopropane-2-glyoxylic acid with H_2O_2 (*Wohlgemuth*, Ann. chimie (9) **3**, 141).

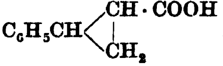
2,2-Dimethyl-cyclopropane carboxylic acid  $(CH_3)_2C<\begin{array}{l}CHCOOH\\ |\\ CH_2\end{array}$, b.p. 100°/10 mm., has a strong odour of butyric acid; *amide* m.p. 177°. The ester, b.p. 90°/15 mm., is obtained by removing HBr from 3,3-dimethyl-γ-bromobutyric ester (*Blanc*, C. r. **145**, 78).

2-Isopropyl-cyclopropane carboxylic acid, $C_7H_{12}O_2$, b.p. 115°/15 mm. (*ethyl ester*, b.p. 95—100°/15 mm ; *amide*, m.p. 167°) has been obtained by the general method 1b, p. 18 from β-isopropyl-γ-bromo-butyric ester (*Blanc*, C. r. **145**, 78).

β-Cyclopropyl-α-alkyl-propionic acids of the general formula $C_3H_5CH_2CHRCOOH$ (R = amyl to tetradecyl) are obtained from cyclopropylmethyl bromide and Na-alkyl-malonic esters (*Arvin*, *Adams*, Am. **50**, 1983). The decyl and undecyl derivatives attack *Mycobact. leprae* and in this resemble the corresponding acids of the cyclopentane series.

2-Isobutenyl-3,3-dimethyl-cyclopropane-1-carboxylic acid, *d*, *l*-chrysanthemic acid (p. 483), b.p. 145–146°/13 mm., cis acid m.p. 115–116°

$(CH_3)_2C<\begin{array}{l}CH\cdot CH:C(CH_3)_2\\ |\\ CH\cdot COOH\end{array}$. The esters are formed from diazo-acetic ester and 1,1,4,4-tetramethyl-butadiene (*Staudinger*, Helv. **7**, 390). Other cyclopropane carboxylic acids with unsaturated alkyl side chains have also been described (ibid.). Degradation by ozone gives *l*-trans caronic acid (p. 31) and acetone (id., Helv. **7**, 201, 390).

Esters of chrysanthemum-monocarboxylic acid and of the dicarboxylic monomethyl ester (p. 33) with the cyclic alcohol pyrethrolone (p. 58), are known as pyrethrins (constitution see p. 482), and are noteworthy for their insecticidal properties.

2-Phenyl-cyclopropane-1-carboxylic acid, trans form, m.p. 105°,

$C_6H_5CH<\begin{array}{l}CH\cdot COOH\\ |\\ CH_2\end{array}$ has been obtained by reaction 9a (p. 21), the addition

of diazoacetic ester to styrene (vol. III). Degradation results in trans cyclopropane-1,2-dicarboxylic acid (*Buchner*, Ber. **36**, 3784).

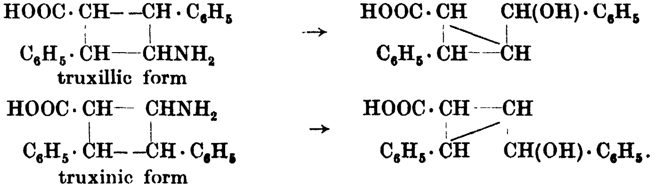
2,3,3-Triphenyl-cyclopropane-1-carboxylic acid has been prepared from diphenyl-diazo-methane and cinnamic ester through the corresponding pyrazoline compound (*Staudinger*, Ber. **49**, 1928).

1-Phenyl-1-cyanocyclopropane, b.p. 99°/1 mm., has been prepared from benzyl cyanide and ethylene-chlorobromide with $NaNH_2$ (*Knowles, Cloke*, Am. **54**, 2028).

Hydroxy Acids: **α-Cyclopropyl-α-hydroxypropionic acid** $CH_3(C_3H_5)\cdot C(OH)\cdot COOH\cdot {}^1/_2\,H_2O$, m.p. 54–55°, anhydrous m.p. 75·5°, is formed from 1-methyl-1-cyclopropyl-ethylene with $KMnO_4$, together with acetyl-cyclopropane (cf. above) (*Kishner*, C. 1911 II 363).

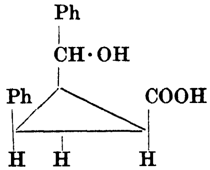
3-BENZOXYL-2-PHENYL-CYCLOPROPANE-1-CARBOXYLIC ACIDS

These acids are degradation products of α-, γ- and ε-truxillic acids (p. 41) and of β- and δ-truxinic acids (p. 42). The method is as follows: the amido-acids are converted by hypochlorite solution into amino acids, which are treated with nitrosyl bromide; the ring is opened and lactones containing the cyclopropane ring are formed; finally, the lactones are converted into hydroxy-acids. The transformation of truxillic and truxinic acids into benzoxyl-phenyl-cyclopropane-monocarboxylic acids is illustrated by the formulae:

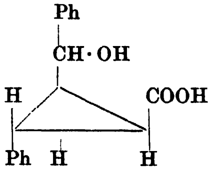


For the course of the reaction in individual cases see *Stoermer*, Ber. **60**, 2573; **64**, 2785. These hydroxy-acids contain four asymmetric carbon atoms in structurally different positions. Eight racemic forms are possible, which have the configurations Ia, Ib, IIa, IIb, IIIa, IIIb, IVa, IVb shown below. The eight acids are represented by the following four formulae, each of which includes an a- and a b-form distinguished by the alternative arrangements of the secondary alcoholic group, not indicated here (*Schenck*, J. pr. **134**, 230).

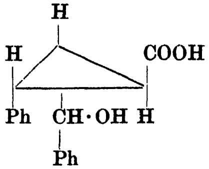
Ia, b



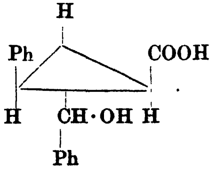
IIa, b



IIIa, b

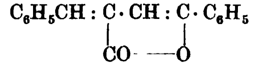


IVa, b



The asymmetry of the carbon atom carrying the hydroxyl disappears when it is oxidised to a carbonyl group, and each pair of a- and b-hydroxy-acids must give one and the same keto-acid. The four racemic isomers are all known (p. 29). By ring fission, known aromatic acids have been obtained from both hydroxy and keto acids (*Stoermer*, Ber. **61**, 2312).

The main degradation product of γ-truxillic acid is the lactone of I a, together with a very small amount of the lactone of I b and greater amounts of the lactones of II a and II b. II b is the only degradation product of ε-truxillic acid. Potash changes the hydroxy-acid I a into the hydroxy-acid III a which does not form a lactone. The same hydroxy-acid is formed together with the lactone of the hydroxy-acid II b and α-benzoxyl-β-benzylidene-propionic acid m.p. 148—149° by degradation of α-truxillic acid (id. Ber. **64**, 2785). In addition to these lactones 1-benzylidene-3-phenyl-isocrotonic lactone m.p. 152° is formed:



$$C_6H_5CH : \underset{\displaystyle CO\text{—}}{C}\cdot CH : \underset{\displaystyle \text{—}O}{C}\cdot C_6H_5$$

The position of the residues COOH, Ph, PhCHOH (benzoxyl), above or below the cyclopropane ring, is indicated in the names of the acids given below by the indices c = cis and t = trans attached to the number indicating the position in the ring.

3^c-Benzoxyl-2^c-phenyl-cyclopropane-1^c-carboxylic acid, —I a—, m.p. 145–146° decomp., lactone m.p. 133·5–134°, converted by vacuum distillation into trans-trans α,δ-diphenyl-α,γ-butadiene m.p. 152–153°. Methyl ester m.p. 124–125°.

3^c-Benzoxyl-2^c-phenyl-cyclopropane-1^c-carboxylic acid, —I b—, m.p. 171–172° decomp., methyl ester m.p. 171–172°, lactone m.p. 168–169°.

3^c-Benzoxyl-2^t-phenyl-cyclopropane-1^c-carboxylic acid, —II a—, m.p. 122° efferv., lactone m.p. 120–121°, methyl ester m.p. 73–74°.

3^c-Benzoxyl-2^t-phenyl-cyclopropane-1^c-carboxylic acid, —II b—, m.p. 153° decomp., lactone m.p. 115°, methyl ester m.p. 86–87°.

3^t-Benzoxyl-2^t-phenyl-cyclopropane-1^c-carboxylic acid, —III a—, m.p. 185–186° decomp., from lactone I a by alcoholic potash and from α-truxillamido acid. Methyl ester m.p. 75–76°.

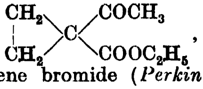
3^t-Benzoxyl-2^t-phenyl-cyclopropane-1^c-carboxylic acid, —III b—, m.p. 188–189°, methyl ester m.p. 104–105°.

3^t-Benzoxyl-2^c-phenyl-cyclopropane-1^c-carboxylic acid, —IV a—, m.p. 152–153°, methyl ester m.p. 124–126°.

3^t-Benzoxyl-2^c-phenyl-cyclopropane-1^c-carboxylic acid, —IV b—, m.p. 151–152°, methyl ester m.p. 82–83° and 125–126°.

KETONIC ACIDS

1-Methyl-cyclopropyl-2-glyoxylic acid, b.p. 100–101°/17 mm., is prepared from 1-methyl-2-propionyl-cyclopropane with $KMnO_4$ (*Wohlgemuth*, Ann. chimie (9) **3**, 141).

1-Acetyl-cyclopropane-1-carboxylic ester,  , m.p. 195°, from sodium-aceto-acetic ester and ethylene bromide (*Perkin*, Ber. **17**, 1440).

1,1-Dimethyl-2-acetonyl-cyclopropane-3-carboxylic acid, $C_9H_{14}O_3$, an oil, from the dihydroxy-acid from Δ^3-carene, p. 247 (*Simonsen*, J. **123**, 549).

2,2-Dimethyl-3, γ-ketobutyl-cyclopropane-1-carboxylic acid (formula I, p. 248), m.p. 78–79°, obtained by oxidative degradation of Δ^4-carene, or synthetically by condensing methyl-heptenone with diazo-acetic ester (*Owen, Simonsen*, J. **1932**, 1424).

1-Isopropyl-2-acetyl-cyclopropane-1-acetic acid, *α-tanacetonic acid, thuja-keto-acid*, $C_{10}H_{16}O_3$, m.p. 75°, ethyl ester b.p. 83–84°/0·2 mm., arises from oxidative ring fission of thujone (tanacetone p. 242) with $KMnO_4$ (*Semmler*, Ber. **36**, 4367). Further degradation gives α-tanacetone-dicarboxylic acid $C_9H_{14}O_4$ p. 32. With chloro-acetic ester and a subsequent *Dieckmann* condensation, the ring can be closed and thujone (semicarbazone m.p. 172°) regenerated (*Ruzicka*, Helv. **15**, 944).

1-Benzoyl-cyclopropane-1-carboxylic acid, m.p. 148°. Its ester is formed by the interaction of benzoyl-acetic ester, ethylene bromide and Na (*Haller*, C. r. **154**, 1567; *Kishner*, C. 1912 I 1458).

3-Benzoyl-2-phenyl-cyclopropane-1-carboxylic acids have been prepared by oxidising the corresponding benzoxylic acids (p. 27) or their methyl esters with chromic acid in AcOH, or by removal of CO_2 from the corresponding dicarboxylic acids which have the two carboxyls on the same carbon atom. Condensation of chalkone with diazo-acetic ester yields the same compounds by way of the pyrazoline derivatives. The 3-ring is opened by HCl (*Kohler*, Am. **41**, 1093). The Roman numerals in the following paragraphs refer to diagrams p. 27.

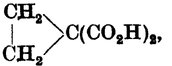
3^c-Benzoyl-2^c-phenyl-cyclopropane-1^c-carboxylic acid, —I—, m.p. 157°, decomp. Methyl ester, m.p. 115–116°, by oxidation of the methyl ester of the hydroxy-acid Ia.

3^c-Benzoyl-2^t-phenyl-cyclopropane-1^c-carboxylic acid, —II—, m.p. 174°. Methyl ester, m.p. 92°, from the esters of hydroxy-acids IIa and IIb. Ethyl ester m.p. 103° from the pyrazoline-carboxylic ester which is formed, together with 4,6-diphenyl-pyrone, by the addition of diazo-acetic ester to benzylidene-acetophenone (id. Am. **41**, 1093).

3^t-Benzoyl-2^t-phenyl-cyclopropane-1^c-carboxylic acid, —III—, m.p. 153–154°, from 3-benzoyl-2-phenyl-cyclopropane-1,1-dicarboxylic acid (id. Am. **39**, 1404). Methyl ester, m.p. 66–67°, from the methyl ester of the hydroxy-acid IIIa.

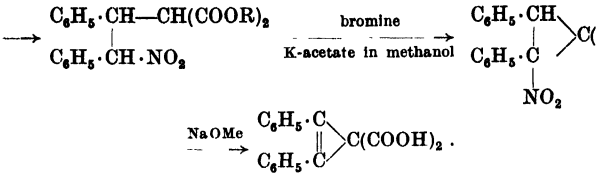
3^t-Benzoyl-2^c-phenyl-cyclopropane-1^c-carboxylic acid, —IV—, m.p. 136–137°, from the methyl ester of keto-acid I by alcoholic potash. Methyl ester, m.p. 66–67·5°.

POLYCARBOXYLIC ACIDS

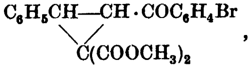
Cyclopropane-1,1-dicarboxylic acid, vinaconic acid, 
$\left.\begin{array}{l}CH_2\\ |\\ CH_2\end{array}\right\rangle C(CO_2H)_2$, m.p. 140°, is prepared by method 5, p. 19, (*Dox*, Am. **43**, 2097) or from the mononitrile by the steps: ester, bromide (*Allen*, Can. J. Res. **9** (1934), 159). HBr converts it into bromo-ethyl-malonic acid, $BrCH_2CH_2 \cdot CH(CO_2H)_2$; it adds on bromine slowly (*Fittig, Marburg*, Ber. **18**, 3413), but is unattacked by nascent hydrogen, HNO_3 or $KMnO_4$ (*Buchner*, Ber. **23**, 704; *Marburg*, Ber. **28**, 8; Ann. **294**, 92). The ester gives butane-tetracarboxylic ester on condensation with sodio-malonic ester, thus behaving like an α,β-unsaturated ester (I 667; *Bone, Perkin*, J. **67**, 108). For the constitution of vinaconic acid and its homologue, **methyl-vinaconic acid,** see *Marburg*, Ann. **294**, 89.

1-Cyano-cyclopropane-1-carboxylic acid, m.p. 149°, from sodio-cyanoacetic ester and ethylene bromide, see *Carpenter, Perkin*, J. **75**, 921.

2,3-Diphenyl-cyclopropene-1,1-dicarboxylic acid, $C_{17}H_{12}O_4$, m.p. 190°, dimethyl ester, m.p. 142°, has been prepared from benzylidene-malonic ester and phenyl-nitro-methane, and also by condensing nitro-stilbene and malonic ester, by the steps

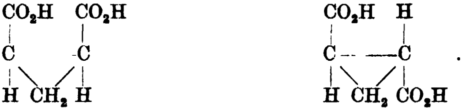


The constitution is proved by the degradation with $KMnO_4$ to dibenzoylmethane, m.p. 77° (*Kohler*, Am. **53**, 1117).

Cyclopropane-keto-1,1-dicarboxylic acids,  , with an aromatic keto group, are formed in the condensation of bromo-substituted unsaturated acetophenones, e.g. benzylidene-p-bromo-acetophenone, with malonic ester and $NaOCH_3$. Ring closure is achieved by means of $Mg(OEt)_2$. Two forms exist, m.ps. 104° and 113° (id. Am. **39**, 2405).

3-Benzoyl-2-phenyl-cyclopropane-1,1-dicarboxylic acid evolves CO_2 on heating, to form the keto-monocarboxylic acid III p. 29. The dimethyl ester, m.p. 92°, is formed by elimination of HBr from (α'-phenyl-β'-bromo-β'-benzoyl)-ethyl-malonic methyl ester (id. Am. **39**, 1404). **3-Methyl-3-benzoyl-2-phenyl-cyclopropane-1,1-dicarboxylic acid,** m.p. 175–178°, is obtained similarly via its dimethyl ester, m.p. 101°. The starting materials for these synthesis are obtained by adding dimethyl malonate either to benzal-acetophenone or to benzal-propiophenone (id. Am. **41**, 992).

Cyclopropane-1,2-dicarboxylic acid. Two isomers, are known, which are the cis and trans forms (*Baeyer*, Ann. **245**, 128):



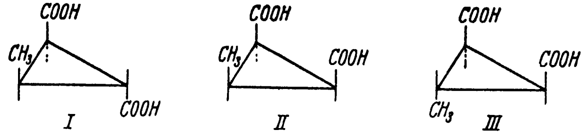
cis form trans form

Cyclopropane-1,2-dicarboxylic acid, cis m.p. 139°, anhydride m.p. 59° is prepared from cyclopropane-1,1,2-tricarboxylic or 1,1,2,2-tetracarboxylic acid by heating. Its ester results from the condensation of ethylene bromide and malonic ester in presence of NaOEt (*Kuster*, Z. physiol. Ch. **145**, 45).

Cyclopropane-1,2-dicarboxylic acid, trans, m.p. 175°, has been obtained from monobromo-glutaric ester by treatment with alcoholic potash (*Boutwell, Perkin*, Proc. **15**, 241). This acid, like the cyclopropane-1,2,3-tricarboxylic acid described below, can be resolved, by means of its quinine salt, into two optically active components (*Buchner*, Ber. **38**, 3112). Its methyl ester, b.p. about 210°, is prepared from pyrazoline-dicarboxylic-3,5-dimethyl ester by method 9a p. 21, with glutaconic ester as a by-product, or from fumaric ester with diazomethane (*v. Pechmann*, Ber. **27**, 1888). Condensation of 1-phenylbutadiene with diazo-acetic ester and subsequent removal of the benzylidene residue by oxidation gives cyclopropane-1,2-dicarboxylic acid in a similar way. The trans acid is transformed at 300° into the cis anhydride m.p. 57° (*Buchner*, Ann. **284**, 214). The dichloride of the acid, b.p. 102°/12 mm., forms with Na_2O_2 the dicarboxylic peroxide $C_3H_4(CO)_2O_2$, decomp. 85°, which explodes on rapid heating (*Fichter*, Helv. **12**, 1152). The reaction of Na-malonic ester with α, α'-dibromo-glutaric ester results in the ester of **1-bromo-cyclopropane-1,2-dicarboxylic** ester; the free acid melts at 172°. At the same time 1,2,2,3-cyclobutane-tetracarboxylic ester (p. 44) is formed. The brominated acid readily yields **1-hydroxy-** and **1-methoxy-cyclopropane-1,2-dicarboxylic acids** m.p. 206–210° and 121° (*Ingold*, J. **119**, 305; *Ing, Perkin*, J. **127**, 2387).

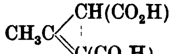
1-Methyl-cyclopropane-1,2-dicarboxylic acids, cis and trans, m.ps. 142° and 168° resp., anhydride b.p. 154–157°/20 mm., are formed from α-methyl-α-bromo- or α-methyl-α'-bromo-glutaric esters with alkali (*Ingold*, J. **127**, 387).

3-Methyl-cyclopropane-1,2-dicarboxylic acid exists in three stereoisomeric forms:



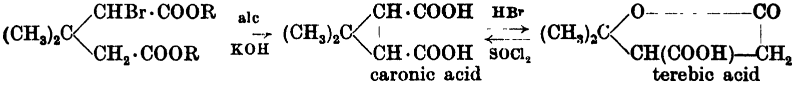
I trans form, m.p. 195° II cis-cis form, m.p. 108° III trans-cis form, m.p. 132°

I and II are formed from 3-methyl-cyclopropane-1,1,2-tricarboxylic ester by hydrolysis and heating with HCl, III in the same way from ethylidene-dimalonic ester through 3-methyl-cyclopropane-1,1,2,2-tetracarboxylic ester (*Goss, Ingold, Thorpe*, J. **123**, 3342).

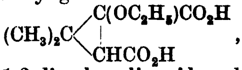
3-Methyl-Δ^2-cyclopropene-1,2-dicarboxylic acid [1],  $CH_3C\begin{cases}CH(CO_2H)\\C(CO_2H)\end{cases}$, m.p. 200° (*Feist*, Ber. **26**, 759), has been resolved, by the aid of brucine and strychnine, into optical isomers, $[\alpha]_D$ + 116° and —128° resp. For a discussion of the constitution of the acid and its esters see *Feist* (Ann. **436**, 135) and *Goss, Ingold, Thorpe* (J. **123**, 327; **127**, 462).

1,2-Dimethyl-cyclopropane-1,2-dicarboxylic acid, cis, m.p. 115–117°, anhydride, m.p. 54–56°; trans m.p. 230–231°, from pyrocinchonic dimethyl ester and diazomethane (*Auwers*, Ann. **511**, 152).

3,3-Dimethyl-cyclopropane-1,2-dicarboxylic acid, *caronic acid*, trans-*d,l* acid, m.p. 213°, is resolved by nor-ψ-ephedrine into a *d*-form m.p. 212°, $[\alpha]_D$ + 34·8° and a *l*-form m.p. 212°, $[\alpha]_D$ − 34·5° (*Owen, Simonsen*, J. **1933**, 1223). It is converted by heating with acetic anhydride into the anhydride of the cis form, m.p. 55°, from which the cis acid is prepared, m.p. 176°, *anil* m.p. 115°. Caronic acid is formed in the oxidation with $KMnO_4$ of carane derivatives, which therefore must contain the cyclopropane ring (p. 248; *Baeyer*, Ber. **29**, 2799. The caronic acids have been synthesised from α-bromo-β, β-dimethyl-glutaric ester by treatment with alcoholic potash (*Perkin, Thorpe*, J. **75**, 48). By heating with hydrogen bromide, caronic acids are readily transformed into terebic acid (p. 255), from which they are regenerated by treatment with $SOCl_2$ in benzene (*Barbier*, C. r. **153**, 188):



caronic acid terebic acid

When α, α′-dibromo-β, β-dimethyl-glutaric ester is heated with alcoholic potash, **ethoxy-caronic acid**  $(CH_3)_2C\begin{cases}C(OC_2H_5)CO_2H\\CHCO_2H\end{cases}$, m.p. 138°, is formed.

1-Isopropyl-cyclopropane-1,2-dicarboxylic acid, *umbellularic acid* $C_8H_{12}O_4$, cis *dl*-form m.p. anhydride 126–127°; *d*- and *l*-forms, m.p. 119–120°; $[\alpha]_D$ + 86·9° and —88·8°; trans *dl*-form, m.p. 197°, *d*- and *l*-forms, m.p. 155°; $[\alpha]_{5461}$ + 232·1° and —236·2° (*Rydon*, J. **1936**, 829; *Ranganathan*, J. Ind. Ch. Soc. **13** (1936), 419). This acid has been synthesised by method 9a (p. 21): the cis form is the final product of the oxidation of umbellulone (p. 245) (*Tutin*, J. **89**, 1104; *Semmler*, Ber. **40**, 5019; **41**, 3988). The trans acid when heated with acetyl chloride gives the anhydride of the cis form, a liquid, b.p. 113°/4 mm.

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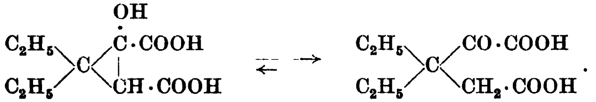
[1] Δ^1, Δ^2, Δ^3 etc. indicate the position of a double bond between C-atom 1, 2, 3 etc. and the following one. Sometimes it is better to use as suffix to the name of the compound a numeral which indicates the position of the double bond, e.g. 2-methyl-cyclopropene-1. The position of the hydroxyl group in an alcohol, or that of the keto group in a ketone is often shown in the same way, e.g. 1-methyl-cyclohexanone-3.

3,3-Diethyl-cyclopropane-1,2-dicarboxylic acids, cis and trans, $C_9H_{14}O_4$, m.ps. 170° and 240° resp. are obtained from α,α'-dibromo-β, β-diethyl-glutaric acid by the action of potash at 150°. The anhydride, a hygroscopic oil, is formed by heating the cis form or treating it with acetic anhydride. (*Deshapande, Thorpe,* J. **121,** 1437). If dibromo-diethyl-glutaric acid is boiled with dilute alkali for about two minutes the corresponding α-hydroxy acid is formed: 3,3-diethyl-cyclopropane-1-ol-1,2-dicarboxylic acid, m.p. 200°. If alkali is slowly added, α-keto-β, β-diethyl-glutaric acid, m.p. 128°, results. In dilute alkali an equilibrium between the two acids is set up slowly (see also *Kon, Stevenson, Thorpe,* J. **121,** 650):



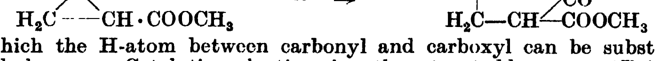
3-cis-Phenyl-trans-cyclopropane-1,2-dicarboxylic acid, $C_6H_5CH\Big\langle\begin{matrix}CHCOOH\\ |\\ CHCOOH\end{matrix}$, m.p. 176°, anhydride, m.p. 134°, *anil* m.p. 193°, is prepared by treating α-bromo-benzylidene-bismalonic ester with alcoholic ammonia, or phenyl-paraconic acid (benzoxyl-succinic lactone) with SO_2Cl_2 in benzene (*Barbier,* C. r. **153,** 188), and also by addition of diazo-acetic ester to cinnamic ester (*Buchner,* Ber. **36,** 3774; *Kotz,* J. pr. 75, 490; *Hardi, Thorpe,* J. **127,** 1237).

3,3-Diphenyl-cyclopropane-1,2-dicarboxylic acid, *diethyl ester,* m.p. 181°, is formed from diphenyl-diazomethane and fumaric ester (*Staudinger,* Ber. **49,** 1938).

3-Phenyl-2-ethoxycyclopropane-1,2-dicarboxylic acid, m.p. 198–199°, is obtained by hydrolysis of β-phenyl-α, α'-dibromo-glutaric ester (*Hardi, Thorpe,* J. **127,** 1237).

3,3-Dimethyl-cyclopropane-1-acetic-2-carboxylic acids, *cis* and *trans homo-caronic acids* $(CH_3)_2C\Big\langle\begin{matrix}CHCO_2H\\ |\\ CHCH_2CO_2H\end{matrix}$, m.ps. 136° and 191° resp., can both be obtained from β-isohexenoic ethyl ester and diazo-acetic ester (*Owen, Simonsen,* J. **1933,** 1225). The cis form is obtained by gentle oxidation of Δ^3-carene (p. 246) and by oxidising 1,1-dimethyl-2-acetonyl-cyclopropane-3-carboxylic acid (p. 28) with alkaline bromine solution (*Simonsen,* J. **123,** 549).

1-Isopropyl-cyclopropane-1-acetic-2-carboxylic acid, *α-tanacetone-dicarboxylic acid,* m.p. 141·5°, is a product of oxidative degradation of sabinene (p. 240; *Wallach,* Ann. **359,** 266; *Semmler,* Ber. **35,** 2045), of sabinol (p. 242; id. Ber. **33,** 1459), and of thujone (p. 242; id. Ber. **36,** 4367). When its dimethyl ester is boiled with $NaOCH_3$ the ring is opened, CH_3OH eliminated, and a 5-membered ring formed,



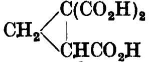
in which the H-atom between carbonyl and carboxyl can be substituted by alkyl groups. Catalytic reduction gives the saturated keto-ester (*Toivonen,* Ann. Acad. Sci. Fenn. **28,** no. 8, 1928). For the formation of tanacetophorone see pp. 57 and 243.

Cyclopropane-1-carboxylic-1, β-propionic acid, m.p. 162°, see p. 156.

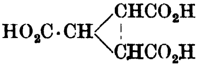
1,1-Dimethyl-cyclopropane-2-carboxylic-3, β-propionic acid $C_9H_{14}O_4$, cis-*d, l*-acid, m.p. 108°; *d*-form isolated by means of nor-ψ-ephedrine, m.p. 112°, [α]D + 37·4°; *l*-form, m.p. 112°, [α]D − 37·1°. The trans *d, l*-acid has been resolved by morphine; *d*-form, m.p. 105°, [α]D + 39°, *l*-form, m.p. 105°, [α]D − 37·8° (*Owen,* J. **1933,** 1223). The racemic cis and trans acids are obtained from methyl-heptenone and diazo-acetic ester by way of the keto-acid, $C_{10}H_{16}O_3$, m.p. 79° (id. J. **1932,** 1424). The cis-*d*-form results from oxidation of Δ^4-carene (*Simonsen,* J. **121,** 2292).

1-Isopropyl-cyclopropane-1-carboxylic-2, β-propionic acid, *homo-tanacetone-dicarboxylic acid,* m.p. 148°, has been obtained from the benzylidene compound of dihydro-umbellulone (Terpenes, p. 245) by ring fission with $KMnO_4$ (*Semmler,* Ber. **40**, 5017; **41**, 3988).

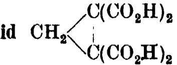
β-(2,2-Dimethyl-cyclopropane-1-carboxylic)-α-methyl-acrylic acid (*chrysanthemum-dicarboxylic acid*), m.p. 164°, *methyl ester,* b.p. 140°/0·5 mm. The methyl ester of this acid has been prepared by hydrolysis of the pyrethrolone ester occurring in chrysanthemum flowers (p. 482). The constitution is deduced from ozonolysis to *l*-trans-caronic acid and pyruvic acid, and from the degradation by ozone of the decarboxylated compound, *2,2-dimethyl-3-propenyl-cyclopropane-1-carboxylic acid,* b.p. 133°/12 mm., which gives *l*-trans caronic acid and acetaldehyde (*Staudinger, Ruzicka,* Helv. **7**, 201; *Yamamoto,* J. Chem. Soc. Japan **44** (1933), 311).

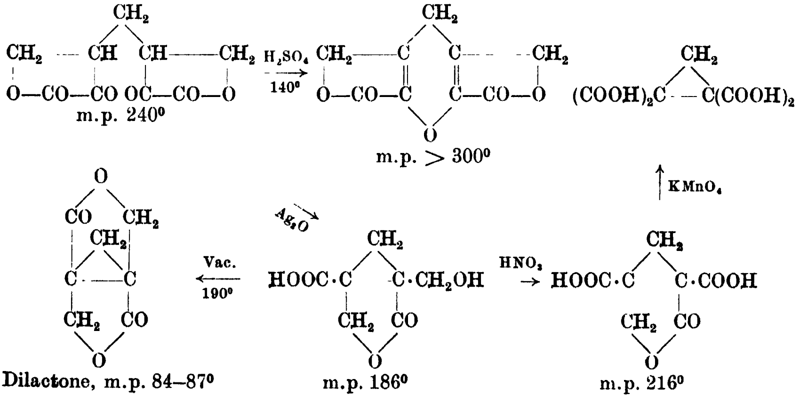
Cyclopropane-1,1,2-tricarboxylic acid,  $CH_2<\begin{matrix}C(CO_2H)_2\\ |\\ CHCO_2H\end{matrix}$, m.p. 187° dec. The *ethyl ester,* b.p. 276°, is obtained from α, β-dibromo-propionic ester (*Conrad,* Ber. **17**, 1187), and from α-bromo-acrylic ester with Na-malonic ester (method 5, p. 19) (*Michael,* J. pr. **35**, 132, 349), and also from the condensation product of camphene (p. 263) and diazo-acetic ester by oxidative degradation (*Buchner,* Ber. **46**, 759).

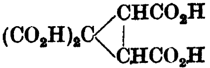
3-Phenyl-cyclopropane-1,1,2-tricarboxylic ethyl ester, b.p. 208–211°/16 mm., from dibromo-hydrocinnamic ester and Na-malonic ester (*Hardi, Thorpe,* J. **127**, 1237).

Cyclopropane-1,2,3-tricarboxylic acid,  $HO_2C\cdot CH<\begin{matrix}CHCO_2H\\ |\\ CHCO_2H\end{matrix}$, cis m.p. 150°—153°, trans m.p. 220°, *anhydride* m.p. 187°, b.p. 265°. The cis acid is prepared from the 1,1,2,3-tetracarboxylic acid (*Perkin,* Ber. **17**, 1652), the trans acid from pyrazoline-3,4,5-tricarboxylic trimethyl ester, which is the adduct of fumaric ester and diazo-acetic ester (*Buchner,* Ber. **23**, 2583); the trans form also results from the oxidation of pseudophenylacetic, or norcaradiene-carboxylic acid (pp. 73 and 165) by $KMnO_4$ (*Braren, Buchner,* Ber. **34**, 995).

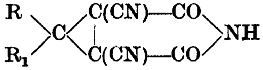
Alkyl-cyclopropane-tricarboxylic acids see *Buchner,* Ber. **27**, 868.

Cyclopropane-1,1,2,2-tetracarboxylic acid  $CH_2<\begin{matrix}C(CO_2H)_2\\ |\\ C(CO_2H)_2\end{matrix}$ melts at 214° with decomp. into the cis 1,2-dicarboxylic anhydride. It has been synthesized from the condensation product of pyruvic acid and paraformaldehyde by the steps shown below (*Feofilaktov,* C. 1930 I 1471). *Ethyl ester* m.p. 43°, b.p. 187°/12 mm., prepared by method 6, p. 20 (*Dressel,* Ann. **256**, 171).

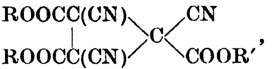


Cyclopropane-1,2,3,3-tetracarboxylic acid , gives cis 1,2,3-tricarboxylic acid between 95° and 100° by loss of CO_2. *Ethyl ester*, b.p. 246°, from dibromo-succinic ester according to method 5, p. 19. The cis-1,2-trans-1,3-acid decomposes at 196–198° (*Buchner*, Ann. 284, 289).

1,1-Dialkyl-2,3-dicyano-cyclopropane-2,3-dicarboxylic acids are known as their imides of general formula



They are prepared from the corresponding dialkyl-dicyano-dibromo-glutarimides (*Guareschi*, C. 1899 II 439; *Peano*, C. 1901 I 582).

Cyclopropane-tricyano-tricarboxylic ester, , m.p. 119°, results from the action of Br_2 or I_2 on Na-cyano-acetic ester in ether, and gives on hydrolysis first cyclopropane-tetracarboxylic, and then 1,2,3-tricarboxylic acid (*Errera*, Ber. **33**, 2979).

2. CYCLOBUTANE GROUP

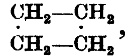
The cyclobutane ring forms part of the complex ring structure of some important compounds of the terpene class. Pinene (p. 250), the main constituent of turpentine oil, is degraded by oxidation to pinic and norpinic acids, two compounds containing the cyclobutane nucleus. Truxillic and truxinic acids, which are isomeric diphenyl-cyclobutane-dicarboxylic acids, occur together with alkaloids in coca leaf. Anemonin, a lactone of cyclobutane-diol-diacrylic acid, occurs in anemone oil as a secondary distillation product.

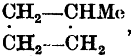
Synthetically, the main ways of preparing cyclobutane compounds are the ring closure method of *Wurtz* and the two malonic ester methods of *Perkin*. Ketones are obtained by distilling barium salts of substituted glutaric acids. Two special methods should be mentioned: one is the condensation of two molecules of ketens, allenes and related compounds, or the condensation of one molecule of such a substance with an olefin, under the influence of light of long wave length (*Staudinger*, Ber. 53, 1092; Helv. 7, 8); cinnamic acid, styrene, stilbene and other unsaturated compounds have been subjected to the same treatment (*de Jong*, Ber. 55, 463; C. 1922 I 745). The other special method of four-ring synthesis consists in the interaction of sodium compounds of substituted glutaric acids with CH_2I_2 or with $COBr_2$ (*Kerr*, Am. 51, 614). Finally, some compounds can be obtained by ring contraction of cyclopentane derivatives or by ring enlargement of cyclopropane derivatives (see ring transitions p. 11).

Short wave radiation depolymerises a number of cyclobutane derivatives into olefins. The theoretical treatment of the isomerism of truxillic and truxinic acids (p. 41) affords a valuable contribution to the stereochemistry of cycloparaffins. The cyclobutane ring is more resistant to HBr, HI, Br_2 or H_2SO_4 than the cyclopropane ring. The ring is always broken between two unequally substituted C-atoms. The compounds give no colour with tetranitromethane in distinction to cyclopropane derivatives (*Filipov*, C. 1915

I 1057). Highly alkylated cyclobutane carboxylic acids are bactericides (*Mycobact. leprae*).

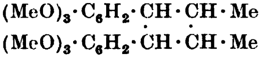
HYDROCARBONS

Cyclobutane  $\begin{array}{c}CH_2\text{—}CH_2\\ \cdot\quad\;\cdot\\ CH_2\text{—}CH_2\end{array}$, *tetramethylene,* b.p. 11–12°, d^0_4 0·7038, is obtained by the ring closure methods quoted above, and also by reducing cyclobutene with H_2 and Ni at 100°; at a higher temperature the ring is split and butane is formed. It has a feeble odour, and burns with a luminous flame. It is stable at ordinary temperatures towards Br_2 and conc. HI. When passed over alumina at 300–350° it is converted into erythrene (I, 116) (*Ostromysslenski,* C. 1916 II 307).

Methyl-cyclobutane  $\begin{array}{c}CH_2\text{—}CHMe\\ \cdot\quad\;\cdot\\ CH_2\text{—}CH_2\end{array}$, b.p. 36–36·5°, from 1-iodo-1-methylcyclobutane with zinc dust and acetic acid; and from cyclobutanealdehyde hydrazone (p. 37) with KOH (*Demjanov,* J. pr. **93**, 179; C. 1913 I 2027).

1,2-Dimethyl-cyclobutane, b.p. 68–70°, is formed together with methylcyclopentane (p. 47) by the action of $AlCl_3$ or $AlBr_3$ on cyclohexane. **Ethylcyclobutane,** b.p. 70°, from the hydrazone of acetyl-cyclobutane with KOH. **1,2-Diisopropyl-cyclobutane,** b.p. 157–158·5°, by catalytic reduction of **1,2-diisopropylidene-cyclobutane,** b.p. 179–181°, obtained from 1,1-dimethylallene by prolonged heating in a sealed tube at 100–225°. **Cyclobutyl-diphenylmethane,** m.p. 39°, by reduction of cyclobutylidene-diphenylmethane, m.p. 58°. (*Kishner,* C. 1911 I 545; 1913 II 2132; *Lebedev,* C. 1911 II 1915; *Zelinsky,* Ber. **65**, 1173).

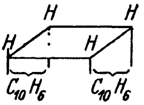
A substance known as *di-asarone* is also a cyclobutane derivative: **1,2-Dimethyl-3,4-di-(2′,4′,5′-trimethoxyphenyl)-cyclobutane**

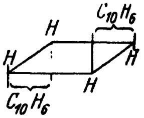


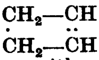
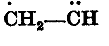
$$\begin{array}{c}(MeO)_3\cdot C_6H_2\cdot CH\cdot CH\cdot Me\\ \qquad\qquad\quad\;\;\cdot\quad\;\;\cdot\\ (MeO)_3\cdot C_6H_2\cdot CH\cdot CH\cdot Me\end{array}$$

m.p. 102°. It is obtained from asarone (vol. III) by HCl in EtOH or from asaryl dibromide with Zn-dust in dilute alcohol. In Et_2O HCl-gas gives an isomer, m.p. 98° (*Haraszti,* Ann. **507**, 201).

Diacenaphthylene $C_{24}H_{16}$, cis m.p. 234°, trans m.p. 307°, is obtained from acenaphthene by the action of light. The spatial arrangement of the aromatic nuclei, relative to the plane of the cyclobutane ring, is different in the two isomers (*Dzievonski,* Ber. **45**, 2491; **46**, 1986):

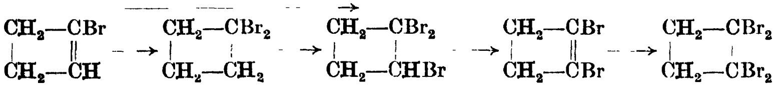




Cyclobutene  $\begin{array}{c}CH_2\text{—}CH\\ \cdot\quad\;\;:\\ CH_2\text{—}CH\end{array}$, an easily liquified gas, b.p. 1·5–2°, d^0_4 0·733, is formed, together with $\Delta^{1,3}$-butadiene, by dry distillation of cyclobutyltrimethyl-ammonium hydroxide (*Willstatter,* Ber. **38**, 1993; **40**, 3985; **41**, 1486); also from ω,ω′-dibromo-2-butylene $BrCH_2CH:CHCH_2Br$ with zinc (*Ostromysslenski,* C. 1916 II 307). When heated it is converted completely into the isomeric erythrene (I, 116). It absorbs bromine to form **1,2-dibromo-cyclobutane,** b.p. 69°/24 mm., m.p. – 2°, from which KOH removes one HBr, giving **bromo-cyclobutene**  $\begin{array}{c}CH_2\text{—}CBr\\ \cdot\quad\;\;:\\ CH_2\text{—}CH\end{array}$, an oil of pungent smell, b.p. 92°, which can be oxidised to succinic acid. Starting from bromocyclobutene *Willstatter* has prepared a number of cyclobutane bromo-substitution products. It combines, e.g., with HBr to give **1,1-dibromo-cyclobutane** (I), b.p. 158°, and with bromine to give **1,1,2-tribromo-cyclobutane** (II), b.p. 109°/19 mm. Dihalogenated cyclobutanes absorb more halogen in the presence of iron powder; the ring is opened and a tetrahalogenated butane is formed (*Willstätter*, Ber. **40**, 3983).

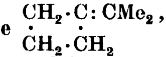
1,1,2-Tribromo-cyclobutane with alcoholic KOH gives **1,2-dibromo-cyclobutene** (III), b.p. 155°, a compound with a strong tendency to polymerise, and which is oxidised by $KMnO_4$ to succinic acid. It gives with bromine **1,1,2,2-tetrabromo-cyclobutane** (IV), m.p. 126°, and with more bromine, first **pentabromo-cyclobutane** $C_4H_3Br_5$, b.p. 175–178°/19 mm., and then **hexabromocyclobutane** $C_4H_2Br_6$, m.p. 186·5° (*Willstatter*, Ber. **40**, 3979). The latter compound crystallises very easily and can be obtained from diacetylene and bromine (*Lespieau*, C. r. **180**, 1347).

(I) (II) (III) (IV)



Methylene-cyclobutane, b.p. 40·6–41·6°, from trimethyl-cyclobutylmethylammonium hydroxide (*Demjanov*, Ber. **55**, 2727), is also formed, together with methyl-cyclobutene, when penterythritol (I, 650) is treated with PBr_3 and the resulting tetrabromide reduced with zinc dust (*Filipov*, C. 1915 I 1057). It gives with HOCl a *chlorohydrin*, b.p. 148°, which forms cyclopentanone (p. 54) with PbO, by a ring enlargement reaction.

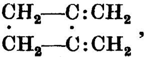
Dimethyl-cyclobutyl-carbinol bromide yields on removal of HBr a hydrocarbon held to be **dimethylmethylene-cyclobutane**



$$\begin{matrix} CH_2\cdot C:CMe_2 \\ \vdots \qquad \vdots \\ CH_2\cdot CH_2 \end{matrix}$$

b.p. 100–102°. Reduction by HI results in ring enlargement and formation of 1,3-dimethyl-cyclopentane.

1,2-Dimethylene-cyclobutane



$$\begin{matrix} CH_2\text{—}C:CH_2 \\ \vdots \qquad \vdots \\ CH_2\text{—}C:CH_2 \end{matrix}$$

, b.p. 63–65°, is obtained by heating allene slowly to 140° (*Lebedev*, C. 1914 I 1410); it gives an amorphous polymerisation product at 150°, and succinic acid on oxidation with $KMnO_4$.

Methylene-cyclobutene, *pirylene*, C_5H_6, b.p. 60°, is formed in the *Hofmann* degradation of piperidine with KOH, through N-dimethyl-piperidine methiodide. That the compound has this constitution has been confirmed by the molecular refractivity (*v. Braun*, Ber. **61**, 1092).

β-Phenyl-cyclobutene $C_{10}H_{10}$, m.p. 25°, is obtained from cinnamylidene-acetic or -malonic ester with BaO (*Doebner*, Ber. **40**, 149).

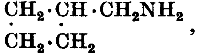
1,3-Diphenyl-cyclobutadiene, $C_{16}H_{12}$, m.p. 130°, is a by-product in the preparation of dibenzyl-methane, together with phenylmethyl carbinol; it arises from the auto-condensation of the acetophenone used under the influence of $NaNH_2$; it is also formed when acetophenone is heated for some time with $NaOC_2H_5$ (*Gastaldi*, Gazz. **44** I 282).

CYCLIC ALCOHOLS

Cyclobutanol, C_4H_7OH, b.p. 123°, *phenylurethane*, m.p. 110–111°, is obtained from aminocyclobutane and nitrous acid, by electrolysing potassium cyclobutane-carboxylate (*Demjanov*, Ber. **40**, 2594, 4962; **41**, 44) or by hydrolysing its ester with cyclobutane-carboxylic acid; the ester is formed by heating the silver salt of the acid with iodine on a water bath. It is oxidised to succinic acid by HNO_3 (id. C. 1911 II 1681). **Cyclobutylamine**, b.p. 80·5–82·5°, is prepared from the amide of cyclobutane-carboxylic acid (p. 38) and NaOCl (*Böeseken*, Rec. **37**, 255), and also by electrolysis of aminocyclobutane-carboxylic acid in alcohol (*Demjanov*, C 1930 I 3297).

EXOCYCLIC ALCOHOLS

Cyclobutyl-carbinol, $C_4H_7\cdot CH_2OH$, b.p. 142°, is obtained by reducing the ester of cyclobutanecarboxylic acid with Na and EtOH, or as a by-product in reducing cyclobutane-dicarboxylic ester with the same agents. (*Zelinsky,* Ber. **46,** 1093); it gives succinic acid on oxidation with HNO_3. *Bromide* b.p. 137—139° (*Demjanov,* Ber. **40,** 4959).

Cyclobutyl-methylamine  $\begin{array}{l}CH_2\cdot CH\cdot CH_2NH_2\\ \vdots\qquad\vdots\\ CH_2\cdot CH_2\end{array}$, b.p. 110°, by reduction of cyclobutyl cyanide, yields with nitrous acid a mixture of methylene-cyclobutane, cyclopentene, cyclobutyl-carbinol $C_4H_7CH_2OH$ and cyclopentanol $C_5H_9\cdot OH$ (id. C. 1903 I 828).

Cyclobutyl-methylcarbinol $C_4H_7\cdot CH(OH)CH_3$, b.p. 144°, is obtained by reduction of cyclobutyl-methyl-ketone.

Cyclobutyl-dimethylcarbinol and **cyclobutyl-diethylcarbinol,** b.p's. 147° and 188°, are formed by the action of $Mg(CH_3)I$ and of $Mg(C_2H_5)I$ upon cyclobutyl-carboxylic ester. When heated with oxalic acid these alcohols undergo ring enlargement to give Δ^1-1,2-dimethyl-cyclopentene and diethyl-cyclopentene resp. **Cyclobutyl-diphenyl-carbinol,** m.p. 54°, b.p. 198°/13 mm., from cyclobutanecarboxylic ester with C_6H_5MgI; *bromide* m.p. 94—95° (*Kishner,* C. 1905 II 761; 1908 II 1342; 1911 I 544; 1912 I 1002).

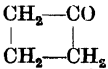
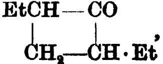
1,1-Dimethylol-cyclobutane $C_4H_6(CH_2OH)_2$ is a viscous oil with a peppermint odour, b.p. 145—147°/20 mm., obtained by reduction of the corresponding dicarboxylic ester with Na + EtOH (*Zelinsky,* Ber. **46,** 1093).

Di-(cyclobutyl-ethyl)-glycol, $[C_4H_7C(OH)C_2H_5]_2$, m.p. 95°, is prepared by reduction of cyclobutylethylketone.

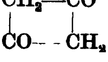
ALDEHYDES

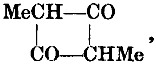
Cyclobutane aldehyde, C_4H_7CHO, b.p. 116—117°, is prepared from calcium cyclobutane-carboxylate and calcium formate (*Perkin,* J. **51,** 238).

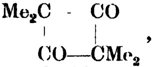
CYCLIC KETONES

Cyclobutanone  $\begin{array}{l}CH_2\text{—}CO\\ |\qquad\;\; |\\ CH_2\text{—}CH_2\end{array}$, b.p. 99°, d_0^0 0·9548, is formed: 1) by the action of bromine and alkali on α-bromo-cyclobutane-carboxylic amide, 2) on boiling 1,1-dibromo-butane with lead oxide and water, 3) from keten and an excess of diazo-methane, instead of cyclopropanone, which would be expected and which is probably an intermediate (*Stoermer,* Ber. **64,** 2823; *Lipp,* Ann. **499,** 20). It is also formed when cyclobutanol or cyclopropyl-carbinol is passed over hot alumina (*Dojarenko,* C. 1926 II 2291). *Semicarbazone,* m.p. 201—202°. It is oxidised to succinic acid by HNO_3 (*Kishner,* C. 1908 I 123). **2,4-Dimethyl-cyclobutanone** and **2,4-diethyl-cyclobutanone**  $\begin{array}{l}EtCH\text{—}CO\\ |\qquad\;\; |\\ CH_2\text{—}CH\cdot Et\end{array}$, m.p. 115—120° and 160—165° resp. These formulae are attributed to substances obtained by distilling Ba salts of α,α′-dimethyl-glutaric and diethyl-glutaric acids (*Jakoviev,* C. 1897 II 342). **2,2,3-Triphenyl-cyclobutanone,** m.p. 135—136°, from diphenyl-keten and styrene, does not react with PCl_5, K in benzene, or phenylhydrazine (*Staudinger,* Helv. **7,** 8).

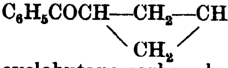
DIKETONES

Dimerisation of ketens gives rise, in general, to the formation of cyclobutane-1,3-diones. **1,3-Cyclobutanedione** = 1,3-diketotetramethylene  $\begin{array}{l}CH_2\text{—}CO\\ |\qquad\;\; |\\ CO\text{—}CH_2\end{array}$, m.p. −7·9 to −7·5°, b.p. 125—126°, is prepared from keten itself by dimerisation, from bromo-acetaldehyde by the action of NMe_3 (*Kotz*, J. pr. **103**, 239), or by heating N-acetylphthalimide (vol. III) to its boiling point (*Hurd, Dull*, Am. **54**, 2432). It is converted into aceto-acetic ester by a trace of H_2SO_4 in EtOH solution, or by $NaOC_2H_5$. Bromine converts it into γ-bromo-aceto-acetyl bromide, which with dry EtOH gives γ-bromo-aceto-acetic ester. With NH_3 acetamide is formed (*Chick, Wilsmore*, J. **97**, 1978; *Staudinger*, Ber. **44**, 535; **53**, 1085; *Schroeter*, Ber. **49**, 2697; **53**, 1917; *Dieckmann*, Ber. **55**, 3331).

1,3-Dimethyl-2,4-cyclobutanedione  $\begin{array}{l}\text{MeCH—CO}\\ \;\;|\qquad\;\; |\\ \text{CO—CHMe}\end{array}$, m.p. 138°, is obtained from the corresponding carboxylic ester by boiling with baryta. The ester is hydrolysed and CO_2 lost (*Schroeter*, Ber. **49**, 2733). Dimerisation of methylketen $CH_3CH{:}CO$ furnishes an impure product, cf. p. 45 (*Staudinger*, Ber. **44**, 542).

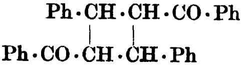
1, 1, 3, 3-Tetramethyl-2,4-cyclobutanedione  $\begin{array}{l}\text{Me}_2\text{C—CO}\\ \;\;|\qquad\;\; |\\ \text{CO—CMe}_2\end{array}$, m.p. 116°, is obtained by the removal of HCl from isobutyryl chloride, by action of "molecular" silver on bromo-isobutyryl chloride, or by heating dimethylmalonic anhydride to 100° in a sealed tube. In the two latter cases dimethylketen (I, 271) seems to be the intermediate, which readily polymerises to tetramethyl-2,4-cyclobutanedione. Its odour recalls both that of menthol and camphor and it also resembles those two substances in its volatility. *Dioxime* m.p. 281° (*Staudinger*, Helv. **8**, 306; Ber. **39**, 970, *Wedekind*, Ber. **39**, 1631). For truxone see p. 46.

EXOCYCLIC KETONES

Cyclobutyl-methyl and cyclobutyl-ethyl ketones, b.ps. 138° and 145° resp., are prepared from the carboxylic chloride with zinc alkyls (*Perkin*, J. **61**, 36) or from the chloride or amide with $Mg(CH_3)I$ (*Zelinsky*, Ber. **41**, 2431; *Kishner*, C. 1913 II 2132). **Dicyclobutyl ketone,** $(C_4H_7)_2CO$, b.p. 205°, is made from the calcium salt of the carboxylic acid. **Benzoyl-cyclobutane**  $\begin{array}{l}C_6H_5COCH—CH_2—CH_2\\ \qquad\qquad\;\; \diagdown_{CH_2}\diagup\end{array}$, b.p. 258° (*Perkin*, J. **61**, 36), from the chloride of cyclobutane-carboxylic acid (see below).

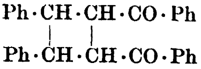
1,2-Dibenzoyl-cyclobutane, m.p. 121–122°, is obtained from 1,2-dibenzoyl-cyclobutene, m.p. 96–97·5°, by catalytic reduction (*Ellingboe*, Am. **56**, 1747).

Diphenyl-dibenzoyl-cyclobutanes, *truxillic* and *truxinic ketones*. When benzylidene-acetophenone (vol. III) is exposed to light, two tetracyclic dimers are formed, which can be separated by means of EtOH or AcOH:



$\begin{array}{l}\text{Ph·CH·CH·CO·Ph}\\ \qquad\;\; |\quad\;\; |\\ \text{Ph·CO·CH·CH·Ph}\end{array}$ m.p. 225–226°

"truxillic ketone"



$\begin{array}{l}\text{Ph·CH·CH·CO·Ph}\\ \qquad |\quad\;\; |\\ \text{Ph·CH·CH·CO·Ph}\end{array}$ m.p. 124°

"truxinic ketone"

The former compound is converted into yet another isomer, m.p. 195° (*Stobbe*, J. pr. **123**, 40, 54) by treatment with sodium acetate and acetic anhydride. For homologous truxinic and truxillic ketones see ib. and *Stobbe*, Ber. **59**, 2254.

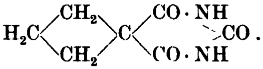
CARBOXYLIC ACIDS

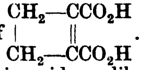
Cyclobutane-carboxylic acid, $C_4H_7CO_2H$, m.p. −6°, b.p. 195°, resembles the fatty acids in odour and is prepared from the 1,1-dicarboxylic acid (see below). Reduction with HI splits the ring, giving n-valeric acid (*Kishner*, C. 1908 II 1342). *Ethyl ester*, b.p. 160°, *chloride*, b.p. 142°, *anhydride*, b.p. 160°, *amide*, m.p. 150–152°, *nitrile*, b.p. 150° (*Freund*, Ber. **21**, 2692; *Carpenter, Perkin*, J. **75**, 921).

2,3- and 2,4-(?) Diphenyl-cyclobutane-1-carboxylic acids, *distyrinic* and *distyranic acids,* m.p. 147 and 176° resp., are obtained from cinnamic acid by boiling with 50% H_2SO_4 (*Stoermer,* Ber. **56,** 1440). For 2,4-diphenyl-cyclobutane-1-carboxylic acid see also p. 42.

2^c, 4^t-Diphenyl-3^c-amino-cyclobutane-1^c-carboxylic acid, m.p. 195–196° decomp. is obtained from *β-truxillamic acid* (p. 41) with NaOCl-solution. *Methylester,* m.p. 83·5–84°. **2^t, 3^t-Diphenyl-4^c-amino-cyclobutane-1^c-carboxylic acid,** m.p. 161°, decomp., is obtained from *β-truxinamic acid,* m.p. 127–128° (*Stoermer,* Ber. **60,** 2575, 2587).

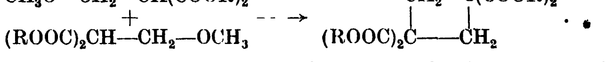
Cyclobutane-1,1-dicarboxylic acid melts at 155° and gives the mono-carboxylic acid. The *ethyl ester,* b.p. 224°, is obtained by method 5, p. 19. The *nitrile-ester,* b.p. 214°, is prepared from trimethylene bromide and sodio-cyanacetic ester (*Kishner,* C. 1905 II 761). With urea and its derivatives cyclobutyl-spiro-triketohexahydro-pyrimidines are formed (*Dox,* Am. **43,** 677):



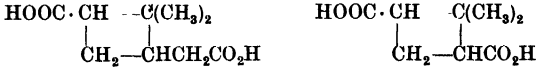
Cyclobutane-1,2-dicarboxylic acid cis occurs in two forms m.p. 91–98° and 139° resp. (*Kuhn,* Helv. **11,** 50, 70, 79, 600). It is prepared from the *anhydride* m.p. 77°, b.p. 271°, obtained from cyclobutane-1,1,2,2-tetra-carboxylic acid by means of acetyl chloride. It is transformed into the trans acid, m.p. 131°, when heated with HCl to 190°. Bromination with Br_2 and P gives 1,2-*dibromo-cyclobutane-dicarboxylic acid,* the ester of which is transformed, by treatment with EtOH and KI, into the ester of  .

Δ^1-Cyclobutene-1,2-dicarboxylic acid, m.p. 178° decomp. This acid readily forms an *anhydride* (*Perkin,* Ber. **26,** 2243; J. **65,** 572, 950; *Bode,* Ber. **67,** 332).

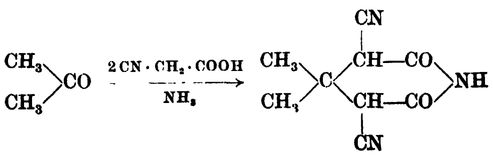
Cyclobutane-1,3-dicarboxylic acids, cis m.p. 155°, *anhydride* m.p. 51°, trans m.p. 171°, have been isolated from the products of the reaction of formaldehyde with malonic ester; they are also obtained from the action of NaOEt on α-chloropropionic ester (*Perkin,* J. **73,** 330). *Simonsen* (J. **93,** 1777) has prepared the same acid by boiling β-methoxy-methyl-malonic ester with conc. HCl. Two molecules of MeOH are split off; the tetra-carboxylic ester so formed is hydrolysed and 2 CO_2 eliminated:

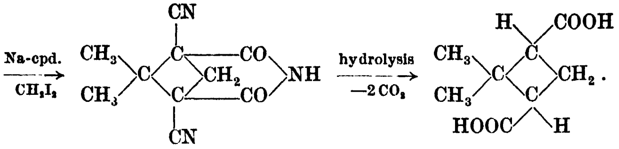


1,1-Dimethyl-cyclobutane-2-carboxylic-4-acetic and -2,4-dicarboxylic acids, *pinic* and *norpinic acids*

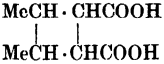


are products of the degradation of *α-pinene* (p. 251). The 1,1-dimethyl-cyclobutane ring with carbon side chains in the 2- and 4-positions is called the *piceane* ring. *Kerr* (Am. **51,** 614) succeeded in synthesising trans-norpinic acid, $C_8H_{12}O_4$, m.p. 146°, in the following way:





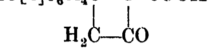
2,3-Dimethyl-cyclobutane-1,4-dicarboxylic acids



$$\begin{array}{l}\mathrm{MeCH\cdot CHCOOH}\\ \quad|\qquad\ |\\ \mathrm{MeCH\cdot CHCOOH}\end{array}$$

. Two such acids result from the elimination of $2\,CO_2$ from 2,3-dimethyl-cyclobutane-1,1,4,4-tetracarboxylic acid (p. 43). *Cis acid* m.p. 87—88°, *cis anhydride* m.p. 50–51°, *trans acid* m.p. 200—201·5° (*Vogel*, J. **1927**, 1985).

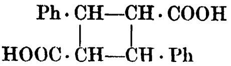
Δ^1-2-(p-Hydroxyphenyl-)cyclobutene-4-one-1-carboxylic acid,



$$\begin{array}{l}\mathrm{HO[4]C_6H_4C{=}C\cdot COOH}\\ \qquad\qquad\ \ |\quad\ |\\ \qquad\quad\ \mathrm{H_2C{-}CO}\end{array}$$

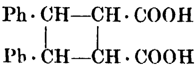
m.p. 224°, has been prepared from phenol and acetone-dicarboxylic acid, and from β-(4-hydroxyphenyl-)glutaconic acid by elimination of water (*Dixit*, J. Univ. Bombay **4** (1935). 153).

Diphenyl-cyclobutane-dicarboxylic acids: Truxillic acids (A) and Truxinic acids (B).



$$\begin{array}{l}\mathrm{Ph\cdot CH{-}CH\cdot COOH}\\ \qquad\ \ |\quad\ \ |\\ \mathrm{HOOC\cdot CH{-}CH\cdot Ph}\end{array}$$

(A)



$$\begin{array}{l}\mathrm{Ph\cdot CH{-}CH\cdot COOH}\\ \qquad\ |\quad\ \ |\\ \mathrm{Ph\cdot CH{-}CH\cdot COOH}\end{array}$$

(B)

History.—In the late eighties of the last century two investigators, *O. Hesse* (Ann. **271**, 180) and *Liebermann* (Ber. **22**, 782), were independently engaged in the study of the bases which occur, together with cocaine, in the leaves of *Erythroxylon coca*, and of the acids obtained by decomposing these bases. *Hesse* discovered the *cocaic* and *β-cocaic acids*, while *Liebermann* isolated two acids which he called *γ*- and *δ-isatropic acids*, assuming them to be isomeric with the known α- and β-acids. The γ-acid was found to be identical with *Hesse's* cocaic acid. Continuing his researches *Liebermann* found his two acids and two more isomers into which they could be converted to be dimeric cinnamic acids, and he introduced the names α-, β-, γ- and δ-truxillic acids for the four compounds. The names are derived from Truxillo, the place where is found a variety of coca rich in γ- and δ-isatropic acids, i.e. α- and β-truxillic acids. He found that the structures of the acids are those shown in (A) and (B) and showed that 11 stereoisomers are theoretically possible. *Riiber* found in 1902 (Ber. **35**, 2908) that ordinary trans-cinnamic acid is transformed by light into α-truxillic acid, and *Stobbe* found, in 1919, an analogous transformation of cis-allocinnamic acid into β-truxillic acid. The configuration of nine isomers was established by the work of *Stoermer* and his co-workers which was begun in 1910. Five of the acids correspond to formula (A), the four others, for which he introduced the name "truxinic", have the formula (B).

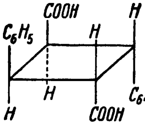
The following general modes of formation of truxillic and truxinic acids are known:

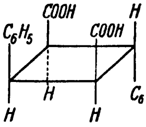
1) Polymerisation of cinnamic and allocinnamic acids by light (*Riiber*, Ber. **35**, 2908; *Ciamician*, ib. 4129; *Stobbe*, ib. **52**, 666; **55**, 2229; **58**, 2416, 2423; *Stoermer*, ib. **54**, 80; *de Jong*, ib. **55**, 463).

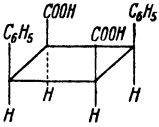
2) The oxidation of photodimeric derivatives, e.g. of cinnamal-malonic acid (*Riiber*, Ber. **35**, 2144; *Stobbe*, Ber. **44**, 870), cinnamal-benzyl cyanide (*Stobbe*, Ber. **45**, 3396; **58**, 85), α-methyl-cinnamal-acetic acid (*Reimer*, Am. **48**, 210).

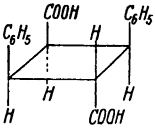
3) Ring synthesis of truxinic acids from 2,3-diphenyl-butane-1,1,4,4-tetracarboxylic ester by means of bromine (p. 44; *Bacher*, Ber. **61**, 543; J. pr. **120**, 301).

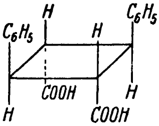
Truxillic acids.—The formulae I—V given below can be used to represent the configurations of the five stereo-isomeric truxillic acids. The four carbon atoms of the cyclobutane ring are not shown, but only the relative positions, above and below the plane of the ring, of the phenyl and carboxyl groups attached to them.

I


II


III


IV


V


I and IV represent trans acids in which the carboxyls occupy positions on opposite sides of the plane, the others are cis acids with the carboxyl groups on the same side. While the cis acids form anhydrides, imides and anils, the trans acids do not. The latter are transformed into the anhydrides of the cis acids by dehydrating agents. Fusion with potash brings about the reverse transformation of cis into trans acids. For the determination of molecular weight, esters of the acids have been used in most cases. All five configurations of truxillic acids can be made to coincide with their mirror images and resolution into optical antimers is impossible. When, however, in I or II one of the carboxyls is converted into either $CO\cdot NH_2$ or $CO\cdot NHPh$ the symmetry is destroyed. *Stoermer* (Ber. 56, 1687, 1693) has succeeded in resolving these amido-acids and anilido-acids into optically active forms. Formulae III, IV and V represent meso forms which cannot be resolved.

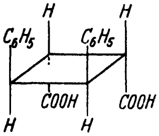
α-**Truxillic acid,** *Hesse's cocaic acid* (I) m.p. 274°, from trans cinnamic acid by the action of light, is reconverted into cinnamic acid by distillation at normal pressure. It has also been prepared by oxidising *diphenyl-cyclobutane-bismethylene-malonic acid* with potassium permanganate (*Riiber*, Ber. **35**, 2411, 2908). The configuration is established by the formation of a truxone (p. 46). It is related to γ-truxillic acid, the anhydride of which is formed by acetic anhydride, and also to ε-truxillic acid, the product of fusion with potash. Aqueous hypochlorite gives with α-truxillamic acid the corresponding *amino-acid*, m.p. 280° decomp.; this with nitrosyl bromide furnishes, apart from 1,4-diphenyl-butadiene, a 3-benzoxyl-2-phenylcyclopropane-1-carboxylic lactone, form IIb (p. 27), a free isomeric acid, form. IIIa, and α-benzoxyl-β-benzylidene-propionic acid m.p. 148–149°. α-*Methyl ester* m.p. 174°, α-*chloride* m.p. 168° decomp.; *d, l-α-amic acid* m.p. 261°; *d, l-α-anilic acid* m.p. 235°, resolved by strychnine or brucine into *d*-α and *l-α-anilic acids* m.p. 205° (*Stoermer*, Ber. **53**, 499; **56**, 1687; **64**, 2783).

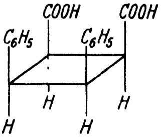
γ-**Truxillic acid** (II), m.p. 228°. The anhydride of this acid is formed when the α-acid is heated either alone or with acetic anhydride; *γ-methylester* m.p. 127°; *γ-anhydride* 191°; *γ-anil* 194°; *d, l-γ-amic acid* 248°, resolved with morphine into *d-γ-* and *l-γ-amic acids* m.p. 258–259°. Treatment with aqueous hypochlorite transforms the *d,l-γ*-amic acid into the corresponding *amino-acid*, m.p. 195–196° decomp. This, under the action of nitrosyl bromide, undergoes ring contraction, and gives a mixture of 3-benzoxyl-2-phenylcyclopropane-1-carboxylic lactones (p. 27). The *d, l-γ-anilic acid*, m.p. 228°, can be resolved by cinchonine into *d-γ* and *l-γ-anilic acids*, also melting at 228°. — *Stoermer* (Ber. **68**, 2102) has recently carried out a step-by-step degradation of γ-truxillic acid to **2,4-diphenyl-cyclobutane-1-carboxylic acid,** m.p. 111°, by means of MeMgI.

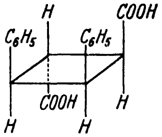
peri-Truxillic acid (III), m.p. 266°, is obtained as an anhydride by heating the α-acid or from the γ-anhydride at 300°; *peri-methylester* m.p. 104·5°; *peri-anhydride* m.p. 287°, *peri-anilic* acid m.p. 247°. **epi-Truxillic acid** (IV), m.p. 285°, is obtained from the peri-acid by boiling it with sodium hydroxide or by heating it with hydrochloric acid to 180°; *epi-methylester* m.p. 111–112° (*Stoermer*, Ber. **57**, 21).

ε-Truxillic acid (*Hesse's β-cocaic acid*) (V), m.p. 192°, results from fusing any of the four other truxillic acids with potash: *ε-methylester* m.p. 64°; *ε-imide* m.p. 198°; *ε-anil* m.p. 252°; *ε-amic acid* m.p. 213°; *ε-dianilide* m.p. 284°. The amic acid is degraded by hypochlorite to *2,4-diphenyl-3-amino-cyclobutane-1-carboxylic acid,* m.p. 188°. — The ε-acid does not form a monomeric, but a vitreous polymeric anhydride (*Stoermer*, Ber. **56**, 1693; **57**, 16, 21; **58**, 2715; **60**, 2576; **68**, 2117).

Truxinic acids.—Six configurations are theoretically possible, I, II and IV representing cis acids, while III, V and VI are trans acids. I and II are meso forms incapable of resolution, III, IV, V, VI are racemic forms which can be resolved. Four are known, termed β-, δ-, ζ- and neo-truxinic acids.

I


II


III


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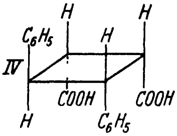
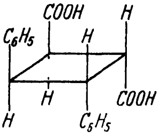
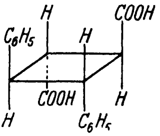


V


VI


β-Truxinic acid, *Liebermann's β-truxillic acid,* (I), m.p. 209–210°, occurs in coca leaves and is formed when the cis cinnamic acids are exposed to light (*Stobbe*, Ber. **52**, 666). It is converted into the δ-acid by fusing it with potassium hydroxide and into the neo-acid by heating it with pyridine or with water. Acetic anhydride reconverts the neo-acid into the β-acid. Oxidation with $KMnO_4$ gives benzil. Its formula cannot be II because it fails to give a truxinone. *β-Methyl ester* m.p. 76°; *β-anhydride* m.p. 116°; *β-chloride* m.p. 96°; *β-anil* m.p. 180°; *β-imide* m.p. 224–225°; *β-amido-acid* m.p. 194°; *β-anilido-acid* m.p. 197°. Though configurations I and II are meso forms, the mono esters, anilides and similar derivatives are racemic. Indeed, *Stoermer* has succeeded in preparing, from the β-anhydride and *l*-menthol, ***hydrogen l-menthyl d, β-truxinate,*** m.p. 208°, and ***hydrogen l-menthyl l, β-truxinate,*** m.p. 149°. *l-Menthyl d, β-truxin-methylanilate,* m.p. 108–109°, yields on careful hydrolysis the dextrorotatary *l, β-truxin-1-methylanilic acid,* m.p. 167 -168°, which is optically active without containing the active *l*-menthyl residue (*Stoermer*, Ber. **59**, 642).

[*d, l*]-**δ-Truxinic acid,** *Liebermann's δ-truxillic acid* (VI), m.p. 175°, is obtained by fusing the β-acid with potassium hydroxide or heating it with conc. hydrochloric acid; also from the ζ-acid by heating it with pyridine. ***d, l-δ-Methyl ester*** m.p. 77°; ***d, l-δ-chloride*** m.p. 78°; ***d, l-δ-amido-acid*** m.p. 189°; ***d, l-δ-anilido-acid*** m.p. 225°. With the aid of cinchonine, δ-truxinic acid can be resolved into optical antimers: ***d, δ-acid*** and ***l, δ-acids,*** m.p. 158–159°; ***l, δ-methyl ester*** m.p. 45°. By reactions similar to those described

for the truxillic acids *d, l-δ*-truxinic acid is converted, through the *amido-acid* m.p. 189°, into the *amino-acid*, m.p. 198°, which with nitrosyl bromide gives 1,4-diphenyl-butadiene tetrabromide, together with *3-benzoxyl-2-phenyl-cyclopropane-1-carboxylic lactone* (p. 27), form II b, the isomeric trans acid III a, and an unsaturated acid melting at 132°; the latter is thought to be impure *α-benzoxyl-β-benzylidene-propionic acid*, which is also obtained from α-truxillic acid and melts, when pure, at 148–149° (*Stoermer*, Ber. **55**, 1872; **64**, 2793).

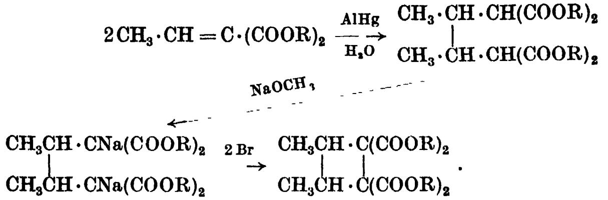
ζ-Truxinic acid, (IV), m.p. 239°, is obtained, as an anhydride, from the δ-acid and from the neo-acid by acetic anhydride or by thionyl chloride (*Stoermer*, Ber. **64**, 2795). Heating with pyridine reconverts it into the δ-acid. Synthetically, the methyl ester has been prepared from methyl 2,3-diphenyl-cyclobutane-1,1,4,4-tetracarboxylate (p. 44) (*Bacher*, Ber. **61**, 543; J. pr. **120**, 301). The ζ-acid is the only cis truxinic acid capable of resolution (by cinchonine), which establishes configuration IV beyond doubt. *d- and l-ζ-*acids m.p. 220°; *d, l-ζ-methyl ester* m.p. 116°; *d, ζ-methyl ester* m.p. 106°; *d, l-ζ-chloride* m.p. 150°; *l, ζ-chloride* m.p. 160°; *d, l-ζ-anhydride* m.p. 150°; *l, ζ-anhydride* m.p. 162°; *d, l-ζ-imide* m.p. 168–168·5°; *d- and l-ζ-imides* m.p. 180°. In accordance with configuration IV, the ζ-acid yields two series of mono derivatives distinguished as a- and b. The melting points are: *mono methyl esters ζ-a* 198°; *ζ-b* 201°; *amic acids ζ*-a 204°, ζ-b 225·5°; *anilic acids ζ*-a 214°, ζ-b 237°; *mono methyl ester acylic chlorides* ζ-b, a 120°; ζ-a, b 104·5°. The constitution of both series is proved by the formation of a ζ-semi-truxinone from the ζ-b-methylester-a-acid chloride with $AlCl_3$ (*Stoermer*, Ber. **58**, 1164).

neo-**Truxinic acid,** (III), m.p. 209°, is found in small amount in the mixture of acids obtained by decomposition of the alkaloids accompanying cocaine. It is formed from the β-acid by heating with pyridine or dimethyl-aniline, or with water to 215–220° in a sealed tube. It is reconverted into the β-acid by heating with acetic anhydride. It has been resolved by means of cinchonine. M.ps.: *d-* and *l-neo-acids* 236–237°; *d, l-neo-methylester* 127°; *d-neo-methylester* 100·5°; *d, l-neo-acyl chloride* 83–84°; *d-neo chloride* 103–104°. The neo-acid, because of its configuration, is capable of giving two series of mono derivatives, denoted by "b" if they relate to the isolated carboxyl in formula III and by "a" if they relate to the other one. M.ps.: *primary methyl esters* neo-a 139°, neo-b 234°; *primary ethyl esters* neo-a 163·5°, neo-b 123°; *amic acids* neo-a 214°, neo-b 213°; *amic methyl esters* neo-a-b 213·5°, neo-b-a 153·5°; *amic ethyl esters* neo-a-b 139°, neo-b-a 142·5°. The constitution is established, as with the ζ-acid, by the conversion of the b-methylester-a-chloride into neo-semitruxinonic methyl ester (see below) (*Stoermer*, Ber. **55**, 1874; **64**, 2800).

1-Cyano-cyclobutane-1,2-dicarboxylic ethyl ester, b.p. 152–154°, is obtained from α, α′-dibromo-adipic ester with NaCN. Hydrolysis gives a **tricarboxylic acid,** which loses CO_2 on heating, yielding a mixture of cis and trans 1,2-dicarboxylic acids, m.ps. 91–98° and 130° (*Kuhn*, Helv. **11**, 600; ***Fuson***, Am. **51**, 1536).

Cyclobutane-1,2,3-tricarboxylic acid, cis m.p. 141–143°, is prepared from cyclobutane-1,1,2,3,3-pentacarboxylic acid (see below) by heating to 190°. The trans acid, m.p. 168–170°, is obtained from the cis by heating with conc. HCl (*Goldsworthy*, J. **105**, 2639). **Cyclobutane-1,1,2,2-tetracarboxylic acid** passes at its m.p., 145–150°, into the 1,2-dicarboxylic acid. The esters are obtained by method 6, p. 20.

2,3-Dimethyl-cyclobutane-1,1,4,4-tetracarboxylic acid, m.p. 138–139°, is obtained from ethylidene-malonic ester, which is reduced by moist aluminium amalgam to *2,3-dimethylbutane-1,1,4,4-tetracarboxylic ethyl ester* b.p. 225–226°/16 mm. The Na-compound of this ester, when treated with bromine, gives *2,3-dimethyl-cyclobutane-1,1,4,4-tetracarboxylic ethyl ester*, b.p. 208–210°/16 mm., from which the free acid is prepared; this by loss of 2 CO_2, yields two stereoisomeric *2,3-dimethyl-cyclobutane-1,4-dicarboxylic acids* (p. 40) (*Vogel*, J. **1927**, 1985):



$$2CH_3\cdot CH=C\cdot(COOR)_2 \xrightarrow[H_2O]{AlHg} \begin{matrix} CH_3\cdot CH\cdot CH(COOR)_2 \\ | \\ CH_3\cdot CH\cdot CH(COOR)_2 \end{matrix}$$

$$\xleftarrow{NaOCH_3}$$

$$\begin{matrix} CH_3CH\cdot CNa(COOR)_2 \\ | \\ CH_3CH\cdot CNa(COOR)_2 \end{matrix} \xrightarrow{2\,Br} \begin{matrix} CH_3CH\cdot C(COOR)_2 \\ | \qquad | \\ CH_3CH\cdot C(COOR)_2 \end{matrix}.$$

2,3-Diphenyl-cyclobutane-1,1,4,4-tetracarboxylic methyl ester, m.p. 148°, is prepared by a method similar to that given for the preceding ethyl ester. Benzylidene-malonic dimethyl ester is reduced with aluminium amalgam to *2,3-diphenyl-butane-1,1,4,4-tetracarboxylic methyl ester.* Two isomers, melting at 163–164° and 167° resp. are obtained. The Na-compound of the lower melting ester gives with bromine *2,3-diphenyl-cyclobutane-1,1,4,4-tetracarboxylic methyl ester*, and this by partial hydrolysis gives the *dimethyl-ester acid* m.p. 203–205° (*Bacher*, Ber. **61**, 543).

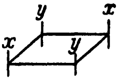
Cyclobutane-1,2,2,3-tetracarboxylic ethyl ester, m.p. 175°, b.p. 195–198°/12 mm. is obtained together with bromo-cyclopropane-dicarboxylic ester from Na-malonic ester and α,α′-dibromo-glutaric ester (*Ing*, J. **1925**, 2387). **Cyclobutane-1,1,2,2,3-pentacarboxylic acid** is a viscous liquid obtained by hydrolysis of its penta-ethylester; the latter, b.p. 230°/20 mm., is prepared from ethane-tetracarboxylic ethyl ester and α,β-dibromo-propionic ethyl ester with Na (*Goldsworthy*, J. **105**, 2639).

CYCLOBUTANE FATTY ACIDS

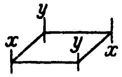
Cyclobutylmethyl-alkylmalonic and **Cyclobutylmethyl-alkylacetic acids.** $C_4H_7CH_2CAlk(COOH)_2$ and $C_4H_7CH_2CHAlkCOOH$. The malonic esters are obtained by condensating cyclobutyl-methylbromide (see above) with alkyl-Na-malonic esters. The n-octyl acid and the higher members up to the n-dodecyl acid attack *Mycobact. leprae,* cf. cyclopentane-carboxylic acids.

Cyclobutane-1,2-diol-1,2-diacrylic dilactone, *anemonin,* has been shown to be the active principle of the oil from *Ranunculus japonica.* The reactions which establish its constitution will be found on p. 479.

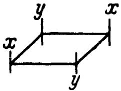
Cyclobutane-2,4-dicarboxylic-1,3-diacetic acid $C_{10}H_{12}O_8$ is known in five isomeric forms, corresponding to the truxillic acids.



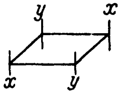
α *m.p. 234°*



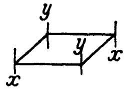
β *m.p. 198°*



γ *m.p. 186°*



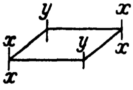
δ *m.p. 207°*



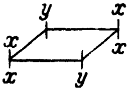
ε *m.p. 223°*

x = ·COOH y = $\cdot CH_2\cdot COOH$

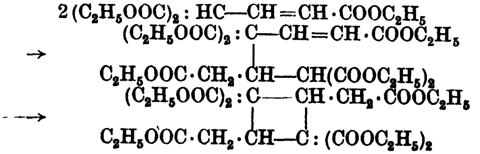
Ingold, Perren and *Thorpe* (J. **121**, 1765) have prepared them by condensing 2 mols. of α-carboxy-glutaconic triethyl ester by means of piperidine. As intermediates, two isomeric cyclobutane-2,2,4,4-tetracarboxylic-1,3-diacetic acids are formed.



α *m.p. 103°*



β *m.p. 87°*



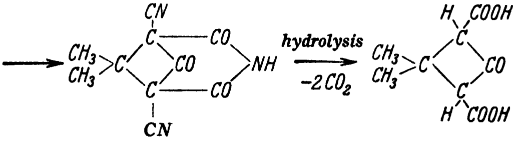
$$2\,(C_2H_5OOC)_2:HC{-}CH=CH\cdot COOC_2H_5$$

$$\rightarrow \begin{matrix} (C_2H_5OOC)_2:C{-}CH=CH\cdot COOC_2H_5 \\ | \\ C_2H_5OOC\cdot CH_2\cdot CH{-}CH(COOC_2H_5)_2 \end{matrix}$$

$$\dashrightarrow \begin{matrix} (C_2H_5OOC)_2:C{-}{-}CH\cdot CH_2\cdot COOC_2H_5 \\ | \qquad | \\ C_2H_5OOC\cdot CH_2\cdot CH{-}C:(COOC_2H_5)_2 \end{matrix}$$

KETO-ACIDS

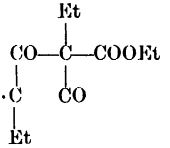
2,2-Dimethyl-cyclobutanone-(4)-1,3-dicarboxylic acid, *keto-norpinic acid,* $C_8H_{10}O_5$, has been synthesised by *Guha* (Current Sci. **2**, 52) in a way similar to that used by him in preparing norpinic acid (p. 253). α,α′-Dicyano-β,β-dimethyl-glutarimide was treated with $COBr_2$. The reaction can be represented as:



Another synthesis carried out by *Guha* (ibid.), is based on the condensation of Na-acetone-dicarboxylic ester with chloro-acetol.

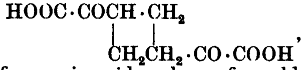
1,3-Dimethyl-cyclobutane-2,4-dione-1-carboxylic methyl ester, m.p. 156–157°, is obtained from symm. dimethylacetone-dicarboxylic methyl ester with conc. sulphuric acid. It behaves as a monobasic acid and is soluble in carbonate solution. *Ethyl ester* m.p. 133–135°. An analogous compound is: **1,3-Diethyl-cyclobutane-2,4-dione-1-carboxylic ethyl ester** m.p. 101·5–102·5°. Both esters give the corresponding diketones when heated with aqueous baryta: **1,3-dimethyl-cyclobutane-2,4-dione,** m.p. 138°, and **diethyl-cyclobutanedione,** m.p. 76–78° (*Schroeter,* Ber. **40**, 1604; **49**, 2697; *Staudinger,* Ber. **50**, 1016).

1,3-Diethylcyclobutane-2,4-dione-1,3-dicarboxylic ester

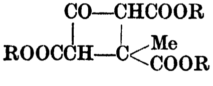


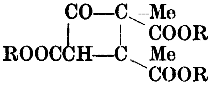
b.p. about 113–116°/"0"mm. This constitution is assigned to the dimeric ethyl-keten-carboxylic ester which can be obtained from bromo-ethyl-malonic ester chloride and zinc, or by the decomposition of propionyl-diazo-acetic ester. When distilled at ordinary pressure the compound depolymerises and the keten is regerated. With aniline the ring is broken and ethyl-malonic anilido-ester is formed (*Chick,* J. **97**, 1978; *Staudinger,* Ber. **42**, 4908; *Schroeter,* ib. **49**, 2697).

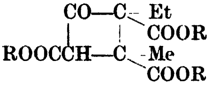
Diacetyl-cyclobutane-dicarboxylic ester is obtained by method 6, p. 20 (*Perkin,* Ber. **19**, 2048).

Cyclobutane-1,3-diglyoxylic acid,  , m.p. 240°, is formed in the condensation of pyruvic acid and paraformaldehyde by conc. sulphuric acid. Hot alkali decomposes it into ethylene and oxalic acid. Hot conc. sulphuric acid converts in into a dilactone (*Kaltwasser,* Ber. **29**, 2273).

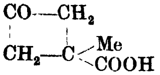
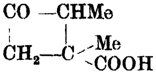
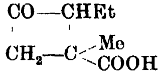
Alkylated cyclobutanone-tricarboxylic esters such as



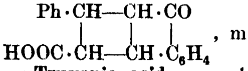


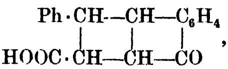


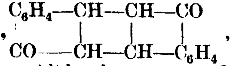
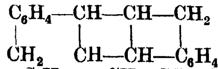
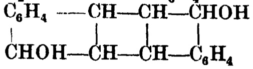
are obtained by condensing sodio-malonic ester, or its methyl or ethyl derivatives, with citraconic ester in EtOH. The first product is presumably an open-chain tetracarboxylic ester which then undergoes cyclic aceto-acetic ester condensation (p. 19). Hydrolysis with hydrochloric acid removes two carbethoxy groups from these compounds and **cyclobutane-1-one-3-carboxylic acids** are formed (*Michael*, Ber. **33**, 3751):

By the loss of one or two molecules of water certain truxillic and truxinic acids become truxonic acids, truxones, and semi-truxinonic acids. The reaction is effected by $AlCl_3$ acting upon the anhydrides or the chlorides of the acids, or on their Me-ester-chlorides. It sheds light upon the configuration of these acids because it only takes place when the reacting groups are adjacent and on the same side of the plane of the cyclobutane ring, whereby a new ring containing the group —C_6H_4·CO— is formed. Hence ε-truxillic and β- and δ-truxinic acids fail to give it.

α-Truxonic acid,  , m.p. 216°; for its configuration see α-truxillic acid. **γ-Truxonic acid,** m.p. 152°; **peri-truxonic acid,** m.p. 221–224°, obtained from peri-truxillic anhydride with $AlCl_3$; **epi-truxonic acid,** m.p. 160°.

ζ-Semi-truxinonic acid,  , m.p. 158°; for the configuration see ζ-truxinic acid; **neo-semitruxinonic acid,** m.p. 224°, gives trans-cinnamic acid on dry distillation; *Me-ester* m.p. 124° (*Stoermer*, Ber. **58**, 1177; **64**, 2802; **68**, 2129).

α- or trans-**Truxone,**  , m.p. 294–295°, (for its configuration see α-truxillic acid) has been prepared from α-truxillic acid and from allocinnamic acid with fuming sulphuric acid, also from α-truxillic chloride with $AlCl_3$. The dimethylether of the *dioxime* melts at 214°. The formation of this truxone furnishes evidence for the configuration of α-truxillic acid. — Reduction with zinc and HCl gives *truxane*  (bis-indene), m.p. 116°, and *truxane-diol*, m.p. 132°,  (*Brass*, Ber. **59**, 1278; *Stobbe*, Ber. **60**, 457).

Peri- or cis-**Truxone,** m.p. 194°, from peri-truxillic acid chloride with $AlCl_3$. *Mono-Ph-hydrazone* m.p. 217° (*Stoermer*, Ber. **68**, 2124).

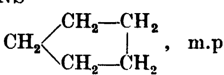
α-Diphenyltruxone, m.p. 253°, and **γ-Diphenyltruxone,** m.p. 224°, are formed when β-phenyl-cinnamic acid and β-hydroxy-p-phenyl-hydrocinnamic acid are treated with fuming sulphuric acid (*Stoermer*, Ber. **52**, 1265).

3. CYCLOPENTANE GROUP

Many more compounds are known which contain five carbon atoms in a ring than three or four. Some are derivatives of cyclopentane and others of cyclopentene. *Cyclopentadiene* occurs in the low boiling fractions of crude benzene from coal tar. Cyclopentanes have been obtained, together with cyclohexanes, from the naphthenes of Caucasian petroleum. Among natural derivatives of cyclopentanone *jasmone*, the odoriferous principle of jasmine, may be mentioned. It is closely related to *pyrethrolone*, the alcoholic component of the pyrethrin insecticides. Derivatives of cyclopentanolones are: *purpurogallin*, occurring in nature as a glucoside dryophanthin, humulic, dihydro-humulic and iso-humulic acids, which are transformation products of humulone and lupulone, the bitter principles of hop, and a transformation product of natural *vulpinic acid*. The *naphthenic acids* from petroleum consist partly of alkylated cyclopentane fatty acids. *Hydnocarpic* and *chaulmoogric acids*, which are important specifics against tuberculosis and leprosy, are natural cyclopentenyl fatty acids with long side chains. *Camphor*, which is readily converted into aromatic substances and contains a five-membered carbon ring termed the *camphoceane* ring, gives rise to many cyclopentane derivatives, such as camphorphorone, camphoric, campholenic and campholytic acids. Camphor and its cyclic transformation products, will, however, be discussed with the hydroaromatic compounds and the terpenes.

Cyclopentane and its derivatives can be obtained by the general methods of ring-synthesis described on p. 18. Cyclohexanes, when heated either by themselves, or with HI under pressure, or with moist $AlCl_3$, are partially transformed into isomeric cyclopentane compounds (*Aschan*, Ann. **324**, 1; *Nenitzescu*, Ber. **66**, 1099), and six-ring ortho-diketones can undergo intramolecular rearrangement to pentacarbocyclic ketones, cf. chloro-cyclopentanedione. This reaction will be met again when considering the degradation of aromatic substances. Similarly, some remarkable cyclopentane derivatives have been obtained from hexahydroxybenzene, viz. *croconic* and *leuconic* acids, which will be discussed in connection with hexahydroxybenzene.

HYDROCARBONS



Cyclopentane, *pentamethylene, R-pentene,* $CH_2\left\langle\begin{array}{l}CH_2—CH_2\\ \qquad\quad |\\ CH_2—CH_2\end{array}\right.$, m.p. —93 to —94°, b.p. 50°, is obtained by reduction of cyclopentyl iodide or of cyclopentadiene (p. 50). Catalytic hydrogenation of cyclopentane with Pt-carbon at 300° leads to ring fission and gives n-pentane, b.p. 36–37° (*Zelinsky*, Ber. **66**, 478, 1419; **68**, 1869).

Homologous cyclopentanes are available in general by the interaction of cyclopentanones with *Grignard* compounds, followed by removal of water and hydrogenation of the cyclopentenes thus formed (id. ib. **66**, 1422).

Methylcyclopentane, m.p. —141°, b.p. 70°, occurs in the so-called hexanaphthene from Caucasian petroleum and in crude Oklahoma petroleum, in the latter to the extent of about 0·2% (*Aschan*, Ber. **31**, 1803; *Hicks-Bruun*, Bureau of Standards J. 7 [1931], 799). It is prepared synthetically from 1,5-dibromohexane, from methyl-cyclopentanone and from tert. methylcyclopentanol (p. 52), and is also formed, with ring contraction, when $AlCl_3$ or $AlBr_3$ act upon cyclohexane until equilibrium is attained (*Aschan*, Ann., **324**, 1; *Zelinsky*, Ber. **65**, 1173; *Nenitzescu*, Ber. **66**, 1099; **69**, 1040). Its action with AcCl$+AlCl_3$ is mentioned on p. 60. For isopropyl-, sec. butyl-, isoamyl-cyclopentane see *Kasansky*, Ber. **69**, 954, 1862.

1,2-Dimethyl-cyclopentane, b.p. 94–98°, two stereoisomers, by catalytic hydrogenation of 1,2-dimethyl-cyclopentene (see below) (*Rysselberge*, Ac. Belg. (5) **12** (1926), 171). **1,3-Dimethyl-cyclopentane,** b.p. 90·7°, from the corresponding ketone, and by hydrogenation of 1,3-dimethyl-cyclopentene, p. 49. The iodide of 1,3-dimethyl-cyclopentane-1-ol (p. 52) is reduced to an optically active *1,3-dimethyl-cyclopentane*, b.p. 91°, $[\alpha]_D$ $+1·78°$. It is oxidised when exposed to the air in diffused light, probably with the formation of a peroxide $C_7H_{14}O_2$. A dimethyl-cyclopentane in which the position of the methyl groups is not known has been found in Borneo petroleum (*Chavanne*, Belg. **31**, 331; **36** (1927), 206).

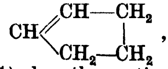
1-Methyl-2-ethyl-cyclopentane, cis b.p. 128°, trans b.p. 121·6° is obtained from 2-ethylcyclopentanone through 1-methyl-2-ethyl-cyclopentane-1-ol (p. 52) → 1-methyl-2-ethyl-Δ^1-cyclopentene, thence by hydrogenating with Pt in glacial acetic acid (*Chiurdoglu*, Ac. Belg. **17** (1932), 1404), and from 1-methyl-2-acetyl-cyclopentane (p. 60) by *Clemmensen's* method (*Nenitzescu*, Bull. **3** (1936), 2209). Optically active form $[\alpha]_D + 4{\cdot}34^0$ (*Zelinsky*, Ber. **35**, 2678). **1-Methyl-3-isopropyl-cyclopentane,** b.p. 140–142·5°/765 mm., from the hydrazone of camphorphorone (p. 305) with KOH (*Zelinsky*, Ber. **62**, 2205). **1,1-Diethyl-cyclopentane,** b.p. 151·5°, from 1,1-diethyl-cyclopentene (p. 49) by hydrogenation with the Zn-Cu couple (*Kishner*, C. 1912 I 1002). Two isomeric **1,2-diethyl-cyclopentanes,** b.ps. 147·5 and 153·5°, are obtained from ethylcyclopentanone with EtMgBr through *1,2-diethylcyclopentanol-1*, b.p. 82°/18 mm., and *1,2-diethyl-Δ^1-cyclopentene*, b.p. 149° (*Chiurdoglu*, Ac. Belg. **17** (1932), 1404; Belg. **42** (1933), 247). **1,2-Dimethyl-3-isopropyl-cyclopentane,** b.p. 159–161°/758 mm., from dihydrocamphorphorone by treatment with MeMgI and subsequent reduction of the tertiary alcohol (p. 52) with Ni at 160° (*Zelinsky*, Ber. **62**, 2205). **n-Hexyl-cyclopentane,** $C_{11}H_{22}$, b.p. 204–206°, from cyclopentanone and n-hexyl-magnesium bromide through *n-hexyl-cyclopentene*, $C_{11}H_{20}$, b.p. 204–205°. **n-Octyl-cyclopentane,** $C_{13}H_{26}$, b.p. 133–134°, from cyclopentanone and n-octyl-MgCl through *n-octyl-cyclopentene*, $C_{13}H_{24}$ (*Zelinsky*, Ber. **66**, 1422). Other alkyl-substituted cyclopentanes: *Eisenlohr*, C. 1926 I 75; *Harris*, Am. **51**, 2591.

Phenyl-cyclopentane, $C_6H_5{\cdot}C_5H_9$, b.p. 213–215°, from ω-Ph-n-amyl chloride with $AlCl_3$ (*v. Braun*, Ber. **45**, 1267; *Stoermer*, ib. **60**, 2557). **1,2-Diphenyl-cyclopentane,** m.p. 47°, and **1,2,3,4-tetraphenyl-cyclopentane** from anhydroacetone- and anhydrodibenzylketone-benzil (*Japp*, *Michie*, J. **79**, 1010; *Henderson*, ib. **79**, 1256). **1,2,3,4-Tetraphenyl-cyclopentane,** m.p. 81°, from the corresponding cyclopentene by reduction with HI and P (*Newman*, Ann. **302**, 231). **Triphenylmethyl-cyclopentane** and **Triphenyldimethyl-cyclopentane** from the corresponding cyclic pinacols (*Abell*, J. **83**, 360, 367). **1-Phenyl-2-cyclopentyl-** and **1-cyclohexyl-2-cyclopentyl-alkanes:** *Denissenko*, Ber. **69**, 2183.

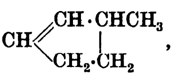
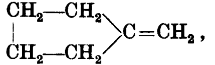
Bromocyclopentane, b.p. 56°/45 mm, from cyclopentanol (*Yohe*, *Adams*, Am. **50**, 1503). **1,2-Dibromo-cyclopentane,** b.p. 71·5°/12 mm., by bromination of cyclopentene (*Zelinsky*, Ber. **66**, 477). **1,2-Diphenyl-3,4-dibromo-cyclopentane,** m.p. 119°, from 1,2-di-Ph-Δ^3-cyclopentene (p. 50) by addition of bromine (*Kishner*, C. 1916 II 318).

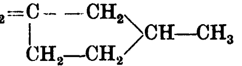
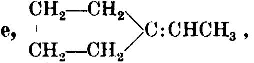
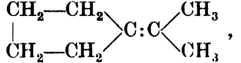
Nitrocyclopentane, b.p. 90–91°/40 mm., d_4^{23} 1·078, can be prepared from cyclopentane with $Al(NO_3)_3$ at 110° in a sealed tube. **1,1-** and **1,2-Methyl-nitrocyclopentanes,** b.pp. 91 and 98–99°/40 mm. (*Nametkin*, C. 1912 I 1702).

Aminocyclopentane, b.p. 106°, is formed in the reduction of cyclopentanone oxime; similarly **β-Methyl-cyclopentyl amine,** b.p. 124–125° (*Sabatier*, C. r. **158**, 985).

Cyclopentene  , b.p. 44·1–44·6°, is obtained from cyclopentanol (p. 51) by the action of dehydrating agents such as $KHSO_4$ (*Godchot*, C. r. **152**, 881), oxalic acid (*Filipov*, C. 1915 I 1057), anhydrous oxalic acid (*Zelinsky*, Ber. **66**, 477), or P_2O_5 (*Auwers*, Ann. **415**, 98); or from halogeno-cyclopentanes with CaO or $BaCl_2$ at 300–400° in a vacuum (Germ.Pat. 255,538). It yields an ozonide $C_5H_8O_3$, which is decomposed by water with the formation of glutaric dialdehyde (*Fischer*, Ber. **65**, 1471). Addition of Ph-azide: *Alder*, Ann. **501**, 8.

Δ^2-Cyclopentenyl chloride, b.p. 25–31°/30 mm., is obtained from cyclopentadiene with HCl at —20° (*Noller*, *Adams*, Am. **48**, 2444). **Perchloro-cyclopentene** C_5Cl_8 m.p. 41° b.p. 283°, is made from hexachloro-cyclopentenone (p. 58) with PCl_5 (*Zincke*, Ber. **23**, 2214) or from xanthogallol (p. 59) with PCl_3 in a sealed tube (*Hantzsch*, Ann. **488**, 203).

Δ²-Methyl-cyclopentene, , b.p. 67°, $[\alpha]_{579}+77{\cdot}9°$, has been prepared by *Semmler* (Ber. **26**, 775) from 3-methyl-cyclopentanol by means of zinc chloride or oxalic acid; **Δ³-methylcyclopentene** is a by-product, b.p. 75–76°. It is also obtained from the iodide by KOH. The oxidation to α-methyl-glutaric acid and the optical activity are evidence for the formula allotted to it (*Zelinsky,* Ber. **35,** 2491; *Godchot,* C. r. **200,** 1599). An isomer of methyl-cyclopentene is , **methylene-cyclopentane,** b.p. 78–81°, a liquid with a penetrating smell of garlic. It is prepared by the removal of CO_2 from cyclopentene acetic acid (p. 65) and is also formed, together with cyclopentanone (p. 54), when calcium cyclopentane-diacetate is distilled (*Kon,* J. **119,** 810). *Nitrosochloride,* m.p. 81°. On oxidation with $KMnO_4$ it gives a *glycol,* m.p. 40°, and cyclopentanone (*Wallach,* Ann. **347,** 325).

1-Methyl-3-methylene-cyclopentane  has been prepared in a similar way from methyl-cyclopentene-acetic acid. It is converted into 1,3-methylcyclopentanone on oxidation (*Zelinsky,* Ber. **34,** 3950; *Tétry,* Bull. **27** (1902), 302). It is optically active like methylcyclopentene; the rotation of the optically active unsaturated five-ring hydrocarbons is much larger than that of the corresponding saturated hydrocarbons. **Ethylidene-cyclopentane,** , b.p. 114°, and **isopropylidene-cyclopentane,** , b.p. 136°, are formed from cyclopentene-isobutyric acid by a shift of the double bond. Alcoholic H_2SO_4 brings about isomeric change into Δ¹-isopropyl-cyclopentene (see below) (*Wallach,* Ann. **353,** 307). **1-Methyl-2-ethylidene-cyclopentane,** b.p. 123–124°, is obtained from methyl-(methylcyclopentyl-)carbinol with KOH (*Godchot,* C. r. **200,** 1599).

1,2-Dimethyl-cyclopentenes. A mixture of a little Δ¹, b.p. 105°, and much Δ², b.p. 96–97°, is formed in the dehydration of 1,2-dimethyl-cyclopentane-1-ol (p. 52) with p-toluene-sulphonic acid (*Chavanne,* Ac. Belg. **12** (1926), 105; *van Rysselberge,* ib. 171). A mixture of the corresponding **1,3-Dimethyl-cyclopentenes** is obtained similarly. The Δ¹-form has been found in resin oil and has been prepared from cyclobutyl-dimethyl-carbinol, $C_4H_9{\cdot}C(OH)(CH_3)_2$, by heating it with oxalic acid, a reaction which involves enlargement of the ring (*Kishner,* C. 1912 I 1002).

1-Ethyl-Δ¹-cyclopentene, b.p. 107°, is prepared from 1-ethyl-cyclopentanol (p. 52) by passing it over Al_2O_3 at 300° (*Chavanne,* Belg. **36,** 591).

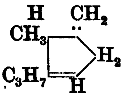
1-Methyl-2-ethyl-cyclopentene, b.p. 127°, is obtained from 1-methyl-2-ethyl-cyclopentane-1-ol (p. 52) by heating with oxalic acid. The product is possibly a mixture of isomers (*Chiurdoglu,* Ac. Belg. **17,** 1404).

Δ¹-Isopropyl-cyclopentene, b.p. 131–133° (see above), also from 1,1-isopropyl-cyclopentanol (*Meerwein,* Ann. **405,** 129). **n-Hexyl-cyclopentene** and **n-Octyl-cyclopentene** see p. 48.

1,1-Diethyl-Δ²-cyclopentene, b.p. 143·5–144·5°, is obtained from the iodide of cyclopentyl-diethyl-carbinol with alcoholic KOH. **1,2-Diethyl-Δ¹-cyclopentene,** b.p. 151–152°, is prepared by similar methods as for the dimethyl compound (*Kishner,* C. 1912 I 1002).

For other alkylated cyclopentenes see *Eisenlohr,* C. 1926 I 75; *Kasansky,* Ber. **62,** 2205; *Richter,* Ber. **64,** 875.

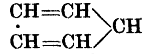
3-Phenyl-Δ¹-cyclopentene, $C_{11}H_{12}$, m.p. 15–16°, b.p. 92–93°/13 mm., has been obtained synthetically from cyclopentyl chloride and PhMgBr (*v. Braun,* Ber. **60**, 2551). **1,2-Diphenyl-Δ³-cyclopentene,** m.p. 15–16°, b.p. 321·5°/747 mm. is prepared by heating the pyrazoline base, $C_{17}H_{16}N_2$, obtained from dibenzylidene-acetone and hydrazine. It is oxidised by $KMnO_4$ to benzoic acid and to the maleinoid form of α, β-di-Ph-glutaric acid (*Kishner*, C. 1916 II 318).



2-Isopropyl-3-methyl-4-methylene-Δ¹-cyclopentene, *chamene*, $C_{10}H_{16}$, b.p. 86–88°/50 mm., *hydrochloride* b.p. 80–90°, occurs in the essential oil from *Chamaecyparis obtusa* leaves (*Chavanne*, Belg. **36** (1928), 591; *Kafuku*, Bull. Chem. Japan **6** (1931), 40, 94).

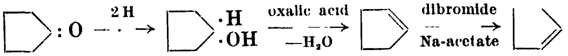
Cyclopentyl-propine and homologues have been prepared by *Gredy*, C. r. **199**, 1129, and alkylenated **Δ¹-cyclopentenes** by *Urion*, Ann. chim. **1** (1934), 5.

Cyclopentadiene, *pentol* (see *Nietzki*, Ber. **22**, 916),



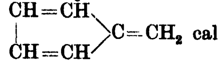
$$\begin{matrix}CH{=}CH\\ CH{=}CH\end{matrix}\!\!>\!CH_2,$$

b.p. 41°, occurs in the first runnings during the distillation of crude benzene from coal tar, from which it is produced industrially (*Horclois*, Ch. et Ind. **31**, spec. No. 4b (1934), 357). It has been synthesised by *Zelinsky* (Ber. **62**, 2865; **66**, 477) from cyclopentanone by the following route:



It is a colourless liquid, violently attacked by alkali as well as by acids, reducing ammoniacal silver solution and rapidly dimerising at ordinary temperature into two *dimolecular cyclopentadienes*, b.p. 88°/35 mm., m.ps. α-form 32°, β-form 19°. Both give on reduction dihydro-dicyclopentadiene, m.p. 51°, and tetrahydro-dicyclopentadiene (cf. ring systems with bridge members p. 188). Their distillation, b.p. 170°, results in a partial regeneration of cyclopentadiene (*Staudinger*, Helv. **7**, 23), a reaction which can be regarded as a reversed diene synthesis (*Wassermann*, Nature **138**, 368). The dicyclopentadienes are much more stable than the monomolecular compound. They are reminiscent of terpenes in their general behaviour, as *Wieland* (Ber. **39**, 1492) and *Rule* (J. **89**, 1339) have pointed out. When heated under pressure cyclopentadiene as well as the dicylopentadienes give higher polymers, viz. *tricyclopentadiene*, m.p. 60°, *tetra-cyclopentadiene*, m.p. 190°, and still higher polymers, from which the monomolecular cyclopentadiene can be partially regenerated (*Stobbe*, Ann. **391**, 151; **446**, 13; *Alder*, ib. **496**, 204; **504**, 216; cf. bridged ring systems p. 188). *Bis-nitrosochloride* of dicyclopentadiene, m.p. 47° (*Wieland*, Ann. **466**, 13). Dicyclopentadiene combines spontaneously with atmospheric oxygen to form a di-peroxide (*Stobbe*, Ber. **52**, 1436). For the addition of Ph-azide to α-dicyclopentadiene see *Alder*, Ann. **501**, 12; and for diene syntheses with the aid of cyclopentadiene see *Diels*, *Alder*, Ann. **460**, 111; **478**, 141; **486**, 202; Ber. **62**, 2350.

The H-atoms in the CH_2-group of cyclopentadiene are characterised by a reactivity similar to those in the group $\cdot CO\cdot CH_2\cdot CO\cdot$, cf. I 470. Potassium in benzene gives *cyclopentadiene-potassium*, a highly reactive compound, which absorbs CO_2 to form the potassium salt of *bis-cyclopentadiene-carboxylic acid* $(C_5H_5\cdot COOH)_2$, m.p. 210° decomp.; *dimethyl ester*, m.p. 85° (p. 190). Cyclopentadiene and oxalic ester condense in the presence of NaOEt to form *cyclopentadiene-oxalic ester* $C_5H_5COCOOEt$. With aldehydes and ketones in the presence of NaOEt coloured hydrocarbons are formed, derived from the hypothetical hydrocarbon

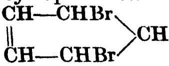
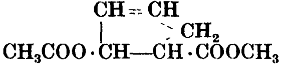
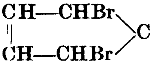


$$\begin{matrix}CH{=}CH\\ |\\ CH{=}CH\end{matrix}\!\!>\!C{=}CH_2$$

called *fulvene*. **Dimethyl-fulvene** $C_5H_4:CMe_2$, b.p. 46°/11 mm., **methylethyl-fulvene** $C_5H_4:CMeEt$, b. p. 185°, are orange-coloured oils. **Diphenyl-fulvene** $C_5H_4:C(Ph)_2$ forms crimson prisms, m.p. 82°; for other fulvenes see *Thiele*, Ann. **348**, 1. Like cyclopentadiene, the fulvenes absorb oxygen, forming peroxides such as $[C_5H_4:C(CH_3)_2]O_4$ (*Thiele*, Ber. **33**, 666; **34**, 68; *Engler*, ib. **34**, 2933).

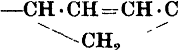
Fulvenes have also been prepared from ionones (p. 125) and cyclopentadiene (*Willstädt*, C. 1934 II 1620; *Kohler*, Am. **56**, 2756).

For the condensation of cyclopentadiene with cyclopentanone and cyclohexanone see *Guillemonat*, C. r. **200**, 1416.

Cyclopentadiene combines with quinones in the molecular proportion 1 : 1. The compounds formed are remarkably stable. **Cyclopentadiene-quinone**, $C_{11}H_{10}O_2$, forms yellowish-green leaflets, m.p. 78° (*Thiele*, Ann. **348**, 31; cf. p. 191). Addition products with hydrogen halides and with halogens are formed in the proportions 1 : 1 and 1 : 2. *Monochloro-cyclopentene* C_5H_7Cl, b.p. 50°/40 mm., *trichloro-cyclopentane* $C_5H_7Cl_3$, b.p. 196°, *tetrachloro-cyclopentane*, $C_5H_6Cl_4$, b.p. 94°/15 mm. Monochlorocyclopentene gives with aniline *anilino-cyclopentene*, C_5H_7NHPh, b.p. 153°/25 mm. and with piperidine *piperidino-cyclopentene*, $C_5H_7 \cdot NC_5H_{10}$, b.p. 94–96°/23 mm. (*Nöldechen*, Ber. **33**, 3348). By the addition of 2 Br to the *conjugated* double bonds of cyclopentadiene (*Thiele*, Ann. **314**, 296), two stereo-isomeric *1,4-dibromides*  arise, one a solid and the other a liquid, which give on oxidation two stereo-isomeric αα′-dibromo-glutaric acids. *Diels* and *Alder* found that the conjugated double bonds of cyclopentadiene readily take up acrolein, maleic anhydride or two molecules of acetoxyl, the latter with formation of  (Ann. **460**, 102; **470**, 63; **478**, 141; **486**, 202; **490**, 236; *Criegee*, ib. **481**, 263). With MeMgI methane is evolved, and bromination of the product of the reaction gi [illegible] romide,  m.p. 60° (*Grignard*, C. r. **158**, 1763

Methyl-ethyl-cyclopentadiene (p. 67) has been [illegible] a the corresponding carboxylic acid. **1-Methyl-3-isopropy** [illegible] **ene-1,3**, C_9H_{14}, a yellow liquid, b.p. 50—55°/20 mm., is easily f [illegible] limination of water from 1-methyl-3-isopropyl-Δ^1-cyclopentene-? [illegible]), which is obtained by heating carvenone with H_2O_2 (*Treibs*, B [illegible] 83).

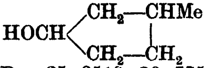
1,2,4-Tri-Ph-cyclopentadiene, 1,2,3,4-tetra-Ph-cy [illegible] **iene, tri-Ph-Me-cyclopentadiene** and **tri-Ph-di-Me-cyclopentadi** [illegible] .ps. 149°, 178°, 163° and 128° are formed from the correspond [illegible] clic pinacols by removal of 2 H_2O (*Newman*, Ann. **302**, 236; *Abell* [illegible] **3**, 360; *Auerbach*, Ber. **36**, 933; *Ziegler*, Ann. **445**, 266; *Dilthey*, J. [illegible]), 1).

Bruson and *Staudinger* (Ind. Eng. **18**, 381) describe the formation of what they call *cyclopentene-caoutchouc*, produced by treating a 25% solution of cyclopentadiene in chloroform with a 15% solution of $SnCl_4$ in the same solvent at 0°. It is possibly the polymer  $(\text{—}CH \cdot \underbrace{CH{=}CH}_{} \cdot CH\text{—})_n$ with CH_2 bridging, and may be analogous to the normal isoprene caoutchouc $(\cdot CH_2 \cdot C \cdot Me{=}CH \cdot CH_2 \cdot)_n$.

RING ALCOHOLS

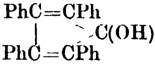
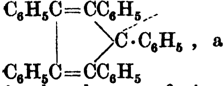
Cyclopentanol, C_5H_9OH, b.p. 140·7°, is prepared from cyclopentanone by reduction with Na and moist ether containing MeOH (*Nenitzescu*, C. 1933 I 1602) or by catalytic hydrogenation (*Zelinsky*, Ber. **66**, 477); it gives cyclopentene (p. 48) by removal of water (*Auwers*, Ann. **415**, 98). *Chloride* b.p. 115°, *bromide* b.p. 137°, *iodide* b.p. 164°, *amine* b.p. 107° (*Wislicenus*, Ann. **275**, 322).

2-Methyl-cyclopentanol-1, cis compound, b.p. 148–149°, *phenylurethane* m.p. 94°, has been obtained from cyclopentene oxide with an excess of MeMgI; trans compound, b.p. 150°, *phenylurethane* m.p. 89°, from the cis form by oxidising it to the ketone and reducing it with Na + Et_2O and potassium carbonate solution (*Godchot*, C. r. **182**, 393).

3-Methyl-cyclopentanol,  , b.p. 49°/12 mm., *amine* b.p. 42°/12 mm., (*Semmler*, Ber. **25**, 3519; **26**, 775): its preparation is similar to that of cyclopentanol. **1- or tert. Methyl-cyclopentanol,** m.p. 36°, b.p. 136° is produced from the corresponding *amine*, b.p. 144°, (which is obtained by reducing the nitration product of methyl-cyclopentane), or from cyclopentanone and MeMgI, or by a direct synthesis from δ-acetobutyl iodide with Mg (p. 18; *Zelinsky*, Ber. **35**, 2684; *Markovnikov*, C. 1899 I 1212).

Analogous reactions of cyclopentanone with various alkyl-Mg-halides have yielded **1-ethyl-cyclopentanol,** b.p. 155°, **1-n-propyl-cyclopentanol,** b.p. 175·5°, **1-isopropyl-cyclopentanol,** b.p. 73°/16 mm., **1-n-butyl-cyclopentanol,** b.p. 195·7°, **1-isoamyl-cyclopentanol,** b.p. 101°/17 mm., and **1-benzyl-cyclopentanol,** b.p. 129°/11 mm. (*Meerwein*, Ann. **405**, 129; *Chavanne*, Belg. **36**, 591; *Harris*, Am. **51**, 2591; *Denissenko*, Ber. **69**, 1668).

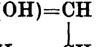
1,2-Dimethyl-cyclopentanol-1, cis-trans mixture, b.p. 145–151°, is obtained from 1-Me-cyclopentene oxide or from 2-Me-cyclopentanone-1 with MeMgI. **1,3-Dimethyl-cyclopentanol-1,** b.p. 144·4°, is prepared from the 3-ketone in the same way (*Chavanne*, Ac. Belg. **12**, 105; Belg. **37**, 141). **1,2,2-Trimethyl-cyclopentanol-1,** b.p. 80–81/49 mm., from 2,2-di-Me-cyclopentanone with MeMgI, gives on treatment with oxalic acid *isolaurolene* = 1,2,2-trimethyl-Δ^5-cyclopentene (p. 313), b.p. 108·5–109° (*Kishner*, C. 1911 I 543). **1-Methyl-2-ethyl-cyclopentanol-1** is made from 2-ethylcyclopentanone (*Chiurdoglu*, Ac. Belg. **17**, 404). **2-Isopropyl-cyclopropanol-1,** cis, b.p. 93–94°/27 mm., *phenylu[illegible]ethane* m.p. 63°, trans, b.p. 84–85°/20 mm., *phenylurethane* m.p. 103°, a[illegible] both prepared from 2-isopropylidene-cyclopentanone-1 through isoprop[illegible] ntanone by reduction, the cis catalytically, and the trans by Na[illegible] *Vavon*, Bull. **43** (1928), 667). **1,2-Dimethyl-3-isopropyl-cyclop[illegible]** . 71–73°/8·5 mm., is obtained from dihydrocamphorpho[illegible] (*Kasansky*, Ber. **62**, 2205). **2,3,4,5-Tetraphenyl-$\Delta^{2,4}$-cyclopen[illegible]** m.p. 140° is prepared from the corresponding ketone (p. 58) by [illegible] with zinc dust, and regenerates the ketone when treated with brom[illegible] al acetic acid (*Dilthey*, J. pr. **139**, 1).

1,2,3,4,5-P[illegible]yl-cyclopentadienol  , m.p. 175–176°, is prepare[illegible] he action of PhMgBr on the ketone just mentioned. By treating the ha[illegible] of this alcohol with Ag in the absence of air *Ziegler* (Ann. **445**, 266) [illegible] ned the free radical **penta-Ph-cyclopentadienyl**  , as small brilliant crimson crystals melting at 260° in the absence of air.

Cyclopentane-1,2-diol, $C_5H_8(OH)_2$, cis form m.p. 29–30°, b.p. 105–106°/10 mm., *bis-phenylurethane* m.p. 197°, trans form m.p. 54–55°, b.p. 99–101°/15 mm., *bis-phenylurethane* m.p. 210°, is obtained from cyclopentene through 1,2-dibromocyclopentane (p. 48) with $AgNO_3$ and subsequent hydrolysis, or through the iodohydrin and the oxide with water at 125° (*Verkade*, Ann. **467**, 221), or from cyclopentene-diol (see below) by catalytic hydrogenation (*Criegee*, Ann. **481**, 263). For the resolution of the trans-diol into antimers by means of aceto-bromo-glucose, $(\alpha)_D \pm 33,8^\circ$, see *Helferich*, Ber. **70**, 308. **Cyclopentene-1,2-oxide,** b.p. 101–102°, is prepared from cyclopentene-1,2-chlorohydrin with KOH, and from cyclopentene with perbenzoic acid. It forms, with *Grignard* compounds, o-substituted secondary alcohols (*Godchot*, C. r. **154**, 1625; **182**, 393; **184**, 208).

1-Methylcyclopentane-1,2-diol, two stereoisomers, mps. 23° and 65°, and cis **1-Phenyl-cyclopentane-1,2-diol,** m.p. 65°, are formed from the corresponding cyclopentenes by treatment with $KMnO_4$ (*Verkade*, Ann. **467**, 217).

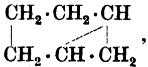
Other glycols of the cyclopentane series have been obtained by the reduction of 1 : 5-diketones (see p. 18), intramolecular pinacol formation taking place.

1-Methyl-cyclopentane-1,2-chlorohydrins, two isomers, one m.p. 35–37°, the other b.p. 50–57°/8 mm., are obtained from 1-Me-Δ^1-cyclopentene with chloro-urea + glacial acetic acid. By shaking this compound with powdered KOH *1-Me-cyclopentene-1,2-oxide*, b.p. 111°, is obtained (*Chavanne*, Belg. **37** (1928), 141). The diacetate of Δ^2-**Cyclopentene-1,2-diol,** b.p. 110–114°/12 mm., results from the interaction of cyclopentadiene with lead tetracetate (*Criegee*, Ann. **481,** 290). **1-Methyl-Δ^2-cyclopentene-1,2-diol** $(CH_3)(OH)\cdot C$  $\left\langle\begin{matrix}C(OH)=CH\\ \qquad\quad\ \ |\\ CH_2\text{———}CH_2\end{matrix}\right.$, b.p. 79–81°/15 mm. is prepared from cyclopentane-1,2-dione with MeMgI (*Godchot*, C. r. **158**, 206).

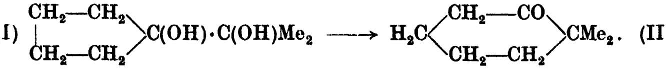
EXOCYCLIC ALCOHOLS

Cyclopentyl-carbinol $C_5H_9CH_2OH$ b.p. 162° is obtained by reducing cyclopentane-carboxylic ester with Na and EtOH, or from cyclopentyl-magnesium chloride and trioxymethylene, or by the action of nitrous acid on **cyclopentyl-methylamine,** $C_5H_9CH_2NH_2$, b.p. 139–145°; in the latter reaction cyclohexanol is also formed, an interesting example of ring enlargement (*Wallach*, Ann. **353**, 325; *Zelinsky*, Ber. **41**, 2629). Oxidation of the alcohol by HNO_3 gives glutaric acid (*Nametkin*, C. 1915 I 1111). *Phenylurethane* m.p. 92–93°, *chloride* b.p. 54–60°/39 mm., *bromide* b.p. 56–57°/17 mm., *iodide* b.p. 71–75°/11 mm. (*Noller*, *Adams*, Am. **48**, 1080). From the iodide *Rosanov* (C. 1916 I 925) obtained the following nitro compounds: *Cyclopentyl-nitromethane* $C_5H_9\cdot CH_2\cdot NO_2$, b.p. 110°/35 mm., *1,1-methyl-nitro-cyclopentane*, $C_5H_8:(Me)NO$, b.p. 86–88°/30 mm., and traces of *nitro-cyclohexane*. *Nametkin* (C. 1916 II 250) found that the action of water on the Mg-compounds derived from the halides gave a mixture of hydrocarbons, of which about 50% were cyclohexene derivatives. **β-Cyclopentyl-ethanol,** $C_5H_9\cdot CH_2CH_2OH$, b.p. 97°/24 mm., is prepared from cyclopentyl bromide, Mg and ethylene oxide, or by the reduction of cyclopentyl-acetic ester (p. 63), obtained by the condensation of cyclopentanone with bromo-acetic ester and subsequent reduction (*Huckel*, J. pr. **142**, 205). *Bromide* b.p. 75–77°/19 mm. — **Cyclopentyl-propanol,** b.p. 85–86°/6 mm., *phenylurethane* m.p. 55°; **β-Δ^2-Cyclopentenyl-ethanol,** b.p. 86–87°/16 mm., has been prepared by *Noller* and *Adams* (Am. **48**, 2444) from Δ^2-cyclopentenyl-acetic ester (p. 65) with Na + EtOH.

Cyclopentenyl-methyl-carbinol, *α-cyclopentyl-ethanol*, $C_5H_9\cdot CHOH\cdot Me$, b.p. 73·5–75°/31 mm., *phenylurethane* m.p. 71–71·5°, is obtained from cyclopentenyl-Mg bromide and acetaldehyde, or from cyclohexene oxide (p. 104) by means of MeMgI, with ring contraction (*Bartlett*, Am. **56**, 2683). — For **cyclopentyl-ethyl carbinols** see *Edwards*, Am. **52**, 3235.

1-Methylol-cyclopentanol-2, $C_5H_8(OH)(CH_2OH)$, b.p. 136–137°/12 mm., is prepared from cyclopentanone-2-carboxylic ester with Na + EtOH. The *dibromide*, $C_5H_8Br\cdot CH_2Br$, when reduced with zinc dust and EtOH, gives *bicyclo-(0,1,3-)hexane, nor-sabinane*  $\begin{matrix}CH_2\cdot CH_2\cdot CH\\ |\qquad\quad\diagup\ \ |\\ CH_2\cdot CH\cdot CH_2\end{matrix}$, b.p. 78·5–79·5°/740 mm. (p. 240) (*Zelinsky*, Bull. **35** (1924), 484).

1-Isopropyl-cyclopentane-1,6-diol, (I), m.p. 62°, b.p. 108°/14 mm., is produced by the action of MeMgI upon 1,1-hydroxycyclopentane-carboxylic ester (p. 67). This pinacol very readily undergoes the pinacolin rearrangement (I, 264, 363), which results in the formation of 2,2-dimethyl-cyclohexanone (II), by migration of one methylene group and enlargement of the ring (*Meerwein*, Ann. **376**, 152):

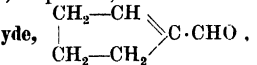
(I)  (II)

Δ^2-Cyclopentenyl-methyl bromide, $C_5H_7CH_2Br$, b.p. 71–72°/16 mm., from the carbinol with PBr_3 (*Arvin, Adams,* Am. **50,** 1790), is important as the starting material for the synthesis of cyclopentenyl-fatty acids (p. 65).

ALDEHYDES

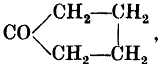
Cyclopentane aldehyde, C_5H_9CHO, b.p. 136°, *semicarbazone,* m.p. 123°, an oil with a penetrating smell reminiscent of valeraldehyde, is prepared from the alcohol with CrO_3 (*Zelinsky,* Ber. **41,** 2629), from iodo-cyclohexanol with $AgNO_3$ by ring contraction (*Tiffeneau,* C. r. **159,** 772), by reducing Δ^1-cyclopentene aldehyde (see below) (*Urion,* Ann. chim. (11) **1,** 5), by dehydrating cyclohexene oxide with ThO_2 or with phthalic anhydride at 330° (*Bedos,* C. r. **188,** 962) or with $MgBr_2 \cdot Et_2O$ (*Clemo,* J. **1933,** 362), and also by the action of dilute sulphuric acid on methylol-cyclopentanol (*Wallach,* Ann. **347,** 326).

1,1-Phenyl-cyclopentane aldehyde, b.p. 134°/15–16 mm., is formed by ring contraction when phenyl-cyclohexene oxide is distilled with sulphuric acid and pumice, or with a trace of $ZnCl_2$. The main product of the reaction is phenyl-cyclohexanone (*Lévy,* C. r. **187,** 45). **1-Phenyl-3-methyl-cyclopentane aldehyde-1,** *semicarbazone,* m.p. 172°, is obtained similarly.

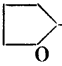
Δ^1-Cyclopentene aldehyde,  $\begin{array}{l}CH_2\text{—}CH\diagdown\\ |\qquad\qquad\quad C\cdot CHO\\ CH_2\text{—}CH_2\diagup\end{array}$, b.p. 48°/11 mm., *semicarbazone,* m.p. 124°, an unstable liquid with an odour resembling that of benzaldehyde, is readily formed by condensation of adipic aldehyde (I 400), by the action of heat on divinyl glycol, and also by loss of HCl from methylene-cyclopentane nitrosochloride and hydrolysis of the oxime so formed by means of dilute acid (*Wallach,* Ann. **347,** 327; *Urion,* Ann. chim. (11) **1,** 5). — An isomeric cyclopentene aldehyde, *semicarbazone,* m.p. 208°, has been prepared from cyclohexene peroxide by *Hock* and *Schrader,* Naturw. **1936,** 159.

RING KETONES

These cyclic ketones are obtained by the methods 7a and 7b given on page 20 from the calcium salts and anhydrides of adipic and alkylated adipic acids. They are, in their turn, the starting materials from which first the corresponding alcohols, and then the saturated and unsaturated pentacarbocylic hydrocarbons are prepared. The oximes of these ketones undergo the *Beckmann* rearrangement in presence of concentrated sulphuric acid to give δ-lactams (I 450).

Cyclopentanone, *ketopentamethylene,*  $CO\langle\begin{array}{l}CH_2\text{—}CH_2\\ \qquad\quad |\\ CH_2\text{—}CH_2\end{array}$, b.p. 130°, occurs in the light wood-tar oils (*Metzner,* Ber. **31,** 1885), and is formed in the ketonic hydrolysis of 2-keto-cyclopentane carboxylic ester, p. 68.

The most convenient method of preparation starts from adipic acid which is heated with catalysts (Germ. Pat. 256,622) such as BaO (*Vavon,* Bull. **43** (1928), 667), $Ba(OH)_2$ (*Thorpe,* Org. Syntheses I, 187), iron filings and a little BaO (*Vogel,* J. **1929,** 721), thorium oxide (*Zelinsky,* Ber. **62,** 2180), or $FeSO_4$ (*v. Braun,* Ann. **490,** 179). Another method is the dry distillation of zinc adipate (*Godchot,* C. r. **182,** 393). Finally, cyclopentanone results from ring enlargement of the chlorohydrin of methylene-cyclobutane with PbO (*Demjanov,* Ber. **55,** 7302), and by ring contraction from cyclohexanone dibromide with aqueous potash; 1,1-cyclopentanol-carboxylic acid, the primary product of the latter reaction, is oxidised to cyclopentanone by means of $PbO_2 + H_2SO_4$. Other alkylated cyclohexanones undergo the same ring contraction, but only when they contain the two bromine atoms in the α,α'-positions, one on either side of the CO-group (*Wallach,* C. 1916 I 365). 1,2-Cyclohexane-dione reacts similarly. Our knowledge of these transformations of brominated cyclohexanones into cyclopentanones is principally due to the work of *Wallach* (Ann. **414,** 296; **437,** 148).

Cyclopentanone smells somewhat like peppermint. Oxidation results in *n*-glutaric acid. Electric moment: 3·00 D. *Oxime* m.p. 58·5° (*Sabatier*, C. r. **158**, 985). When heated with acetic anhydride to 180° it gives *cyclopentenol acetate*, b.p. 156–158°, which is derived from the enolic form. Cyclopentanone and benzaldehyde condense readily to give *monobenzylidene* and *dibenzylidene compounds*, $Ph·CH:(C_5H_6O)$ and $PhCH:(C_5H_4O):CHPh$ (*Mentzel*, Ber. **36**, 1499; *Wallach*, C. 1908 I 637; *Cornubert*, C. r. **190**, 440). The dibenzylidene compound, which crystallises in lemon-coloured needles, is reduced catalytically to a *dibenzyl compound*, m.p. 190°. Cyclopentanone undergoes condensations of a similar kind with phenol-aldehydes (*Sandahl*, J. Pharm. Chim. **19** (1934), 126) and with ketones (*Wallach*, Ann. **394**, 362). Unsaturated ketones of the benzylidene-acetophenone type give, by addition, "semicyclic" ketones, such as —$CH(Ph)·CH_2·COPh$ (*Georgi*, J. pr. **86**, 232).

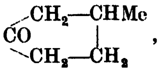
Cyclopentanone and nitrous acid give *di-isonitroso-cyclopentanone*, $HON:(C_5H_4O):NOH$, m.p. 215° (*Borsche*, C. 1909 II 1549). In presence of NaOEt two or three molecules condense to *2-cyclopentylidene-cyclopentanone*, $(C_5H_6O):(C_5H_8)$, b.p. 118°/12 mm., and *2,2'-dicyclopentylidene-cyclopentanone* $(C_5H_8):(C_5H_4O):(C_5H_8)$, m.p. 77°, b.p. 190°/12 mm. (*Wallach*, Ber. **29**, 2962).

When cyclopentanone is halogenated, the halogen atom enters the position next to the CO group (*Kotz*, Ann. **400**, 50). **2-Chlorocyclopentanone-1,** b.p. 80°/10 mm., obtained by exposing cyclopentanone to chlorine in diffused daylight at a temperature not exceeding 25°, gives with $Ba(OH)_2$ *cyclopentanone-1-ol-2*, b.p. 80°/12 mm., and with dimethylaniline *Δ^2-cyclopentene-1-one*, b.p. 135–136°. **Tetrabromo-cyclopentanone,** m.p. 99°, is obtained from cyclopentanone with four molecules of bromine; the position of the Br-atoms is uncertain. HBr is readily eliminated and *tribromo-cyclopentenone* is formed. This with one molecule of Br_2 gives *pentabromo-cyclopentanone*, m.p. 93° (*Godchot*, C. r. **155**, 1522; **156**, 332). Condensation of cyclopentanone with chloroform in the presence of KOH results in the formation of *1-trichloro-Me-cyclopentane-1-ol*, $C_5H_8(OH)CCl_3$, b.p. 102°/10 mm. (*Garland*, Am. **53**, 2414).

Alkylated cyclopentanones are prepared, like the parent ketone, by method 7a p. 20, starting from the corresponding alkylated adipic acids (*Blanc*, Bull. **3** (1908), 780; *v. Braun*, Ann. **490**, 179), or by oxidising the corresponding cyclopentanols (*Kishner*, C. 1911 I 543). *Haller* and *Cornubert* (Bull. **39** (1926), 1724; C. r. **158**, 298, 1616) have prepared methylated cyclopentanones by direct methylation of cyclopentanone with CH_3I and $NaNH_2$. The four H-atoms adjacent to the CO-group can be substituted successively by Me. If the action of $NaNH_2$ in toluene is carried still further the ring is broken and tetra-Me-cyclopentanone is transformed into 2,2,5-trimethyl-caproic amide.

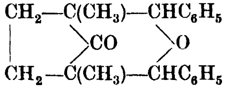
Hintikka (C. 1914 I 789) and *Nametkin* (Ann. **459**, 144) have found alkyl-cyclopentanones among the oxidation products of terpene derivatives, and *v. Braun* (Ann. **490**, 100) has encountered others in degrading naphthenic acids from petroleum.

2-(α)-Methyl-cyclopentanone-1, m.p. –76·1°, b.p. 139·5°, *semicarbazone* m.p. 174°, is prepared from α-Me-adipic acid (*Montemartini*, Gazz. **26** (II) 259), or by boiling 2-Me-cyclopentanone-carboxylic ester with HCl (*Ryssel-berghe*, Ac. Belg. **1926**, 171).

3-(β)-Methyl-cyclopentanone, 
$\mathrm{CO}\!\left<\begin{array}{l}\mathrm{CH_2—CHMe}\\ \qquad\ |\\ \mathrm{CH_2—CH_2}\end{array}\right.$, b.p. 144°, *semicarbazone* m.p. 188° decomp., is prepared by passing β-Me-adipic acid over MnO_2 at 300°, or over BaO at 270° (*Sabatier*, C. r. **158**, 985; *Chavanne*, Ac. Belg. **1926**, 105; *Godchot*, C. r. **192**, 962; *Garland*, Am. **53**, 2414; *Nenitzescu*, C. 1933 I 1602). The optically active form is known, $[\alpha]_D$ +135·9° (*Zelinsky*,

Ber. **35**, 2489). The compound smells like camphorphorone, which also belongs to the cyclopentanone group, but is described later, p. 305. The *oxime* of Me-cyclopentanone is converted by P_2O_5 into the nitrile of hexylenic acid, C_5H_9CN, *β*-Me-pyridine being formed at the same time (*Zincke*, Ann. **299**, 367), cf. the similar behaviour of other cyclic ketones.

Dimethyl-cyclopentanones, $C_7H_{12}O$. Direct methylation of cyclopentanone gives 2-Me-cyclopentanone together with a mixture which consists of 95% of symm. *2,5-(α,α′)-di-Me-cyclopentanone,* b.p. 147°/144 mm., and 5% of asymm. *2,2-(α,α)-di-Me-cyclopentanone,* b.p. 143–144°. *Semicarbazones,* m.ps. 175° and 191°. The *dibenzylidene compound* of the symm. isomer, m.p. 129°, has also been obtained from α,α′-di-Me-adipic acid (*Zelinsky,* Ber. **29**, 403). The *monobenzylidene compound* of the asymm. isomer melts at 36·5–37°. The first isomer combines with two molecules of benzaldehyde to an ethylene-tetrahydropyrone derivative (*Haller,* C. r. **179**, 315; **180**, 1988; **181**, 81):

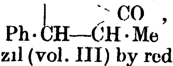


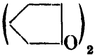
3,4-(β,β′)-Dimethyl-cyclopentane-1-one, b.p. 153–155°, a mixture of two isomers whose *semicarbazones* melt at 175·5–176° and 201–202° resp., is prepared by heating either of the two forms, m.ps. 133° and 104–105°, of *β,β′*-dimethyl-adipic acid with acetic anhydride (*Faltis,* Ann. **433**, 103). **2,3,3-(α,β,β)-Trimethyl-cyclopentane-1-one,** $C_8H_{14}O$, is prepared from α,*β,β*-trimethyl-adipic acid, **2,2,5-(α,α,α′)-trimethyl-cyclopentane-1-one** and **2,2,5,5-(α,α,α′,α′)-tetramethyl-cyclopentane-1-one** by methylation of 2,5-dimethyl-cyclopentanone. **3,3,4-Trimethyl-cyclopentane-1-one,** b.p. 172–174°, *semicarbazone* m.p. 162°, *di-p-nitrobenzylidene* compound m p. 190°, has been prepared by *v. Braun* from the *naphthenic acid* $C_{10}H_{18}O_2$, b.p. 144–145°/14 mm. (p. 65), of Rumanian petroleum (Ann. **490**, 100). Its constitution was established (Ber. **66**, 1499) by converting it into an amine, and then into the *cyclo-olefine,* C_8H_{14}, b.p. 117–123°, which on oxidation with $KMnO_4$ gave *α,β,β-trimethyl-glutaric acid,* $C_8H_{14}O_4$, b.p. 160–170°/0·5 mm.

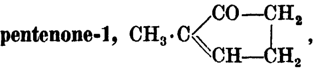
3,3-(β,β)-Methyl-ethyl-cyclopentane-1-one, b.p. 174°, *semicarbazone,* m.p. 170°, is prepared from α-methyl-α-ethyl-tetramethylene bromide with Mg + CO_2; **3,4-(β,β′)-methyl-ethyl-cyclopentane-1-one,** b.p. 180°, *semicarbazone* m.p. 208–209°, from the corresponding adipic acid, and **3-propyl-cyclopentane-1-one,** b.p. 190–191°, *semicarbazone,* m.p. 179°, from propyl-adipic acid (*v. Braun,* Ann. **490**, 179).

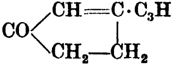
2,5-(α,α′)-Methyl-isopropyl-cyclopentane-1-one, *dihydro-camphorphorone* is obtained from camphorphorone by hydrogenation with Ni at 130° (p. 306) (*Kasansky,* Ber. **62**, 2205).

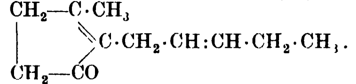
3-Methyl-2-n-amyl-cyclopentane-1-one, *tetrahydropyrethrone, tetrahydrojasmone,* b.p. 100–105°/12 mm., is made by reduction of pyrethrolone (p. 58) or jasmone (p. 57). *Semicarbazones* m.ps. 165–166° and 191–192° (*Staudinger, Ruzicka,* Helv. **7**, 258; *Treff, Werner,* Ber. **66**, 1521; *Ruzicka,* Helv. **16**, 1208). **3-Methyl-5-n-amyl-cyclopentane-1-one,** b.p. 107–109°/4 mm. (*Staudinger, Ruzicka,* Helv. **7**, 248).

2,5-Dimethyl-3,4-diphenyl-cyclopentanone-1,  , m.p. 122°, is obtained from dimethyl-anhydroacetone-benzil (vol. III) by reduction with HI and P, **2,5-dimethyl-3,4-diphenyl-Δ⁴-cyclopentenone-1,** m.p. 122°, being formed as an intermediate product (*Japp, Maitland,* J. **85**, 1473).

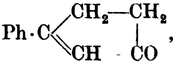
Methylene-3,3′-bis-cyclopentanone, CH_2:  , m.p. 63–64°, has been prepared by *Dieckmann's* ring closure method (*v. Braun,* Ber. **64**, 2621) from methylene-3,3′-bis-adipic acid. The acid was obtained by oxidising 4,4′-dihydroxy-dicyclohexyl-methane.

2-Methyl-Δ^2-cyclopentenone-1, , b.p. 157°, *oxime* m.p. 128°, has been isolated from light wood-tar oil (*Looft*, Ann. **275**, 377), and is prepared synthetically from cyclopentane-1,2-dione with MeMgI. The unsaturated glycol first formed (p. 53) is dehydrated by boiling with aqueous oxalic acid (*Godchot*, C. r. **158**, 506; *Looft*, Ber. **27**, 1538).

3-Isopropyl-Δ^2-cyclopentenone-1, *tanacetophorone*, , b.p. 83·5–84·5/11 mm., *semicarbazone*, m.p. 184–185°, has been found in heavy acetone oil and is made by distilling tanacetone-dicarboxylic acid with soda-lime. On oxidation it gives the lactone of γ-hydroxy-isoheptylic acid (*Semmler*, Ber. **25**, 3350; *Pringsheim*, ib. **58**, 1409). **2-Isopropylidene-cyclopentanone-1,** b.p. 78–79°/10 mm., *oxime*, m.p. 83°, is obtained from cyclopentanone and acetone by means of NaOMe. Catalytic hydrogenation converts it into the saturated ketone (*Vavon*, Bull. **43** (1928), 667; *Cornubert*, ib. **47** (1930), 958).

Jasmone, $C_{11}H_{16}O$, the odoriferous principle of jasmine oil, of which it constitutes 3%, b.p. 108–110°/5 mm, *semicarbazone*, m.p. 206°, *oxime*, m.p. 45°, has been identified as **3-methyl-2(n-pentene-[2′]-yl)-Δ^2-cyclopentene-1-one,** . The constitution has been established by catalytic hydrogenation with Pd to *tetrahydro-pyrethrone*, 3-Me-2-*n*-amyl-cyclopentane-1-one, $C_{11}H_{20}O$, b.p. 91°/7 mm, whose constitution is known (p. 56), since it gives γ-Me-δ-ketodecoic acid and caproic acid and laevulinic acid on oxidation, and has been synthsised by *Staudinger* (Helv. **7**, 236) from γ-bromo-valeric and *n*-amyl-malonic esters. The fact that of the two double bonds one is in the side chain is shown by the oxidation of jasmone to laevulinic, propionic and acetic acids. Gentle reduction of jasmone results in the formation of *dihydrojasmone*, b.p. 101–102°/5 mm., *semicarbazone*, m.p. 175–176°, which still contains the double bond in the ring. This is identical with synthetical *3-Me-2(n-amyl)-Δ^2-cyclopentene-1-one* (*Staudinger*, *Ruzicka*, Helv. **7**, 256; **16**, 1208; *Treff*, *Werner*, Ber. **66**, 1521) and is obtained synthetically from β,γ-hexenol (*Treff*, *Werner*, Ber. **68**, 640).

For compounds resembling jasmone in structure see Brit. Pat. 435,605, 435,608; French Pat. 765,515, 767,725, 785,540, 788,056; Germ. Pat. 613,308, 639,455. For a general method of preparing similar unsaturated pentacarbocyclic ketones from unsaturated aliphatic acids see *Plattner* and *Pfau*, Helv. **20**, 1474.

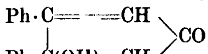
3-Phenyl-Δ^2-cyclopentenone, , m.p. 84°, has been prepared from phenacylacetone (vol. III) with dilute sodium hydroxide. *Oxime* m.p. 147° (*Borsche*, Ber. **41**, 194). For **Tetraphenyl-cyclopentenones** see *Dilthey*, J. pr. **139**, 1.

1,1,3,3-Tetramethylol-cyclopentanone-2, $C_5H_4O{\cdot}(CH_2OH)_4$, m.p. 143°, is prepared from cyclopentanone, formaldehyde and milk of lime. *Tetrabenzoate* m.p. 144° (*Mannich*, Ber. **56**, 833).

1-Methyl-Δ^2-cyclopentene-3-ol-4-one, yellow crystals, m.p. 58–59°, is obtained by hydrolysing the condensation product of β-methyl-glutaric ester and oxalic ester with 20% H_2SO_4. It is reduced to the *saturated hydroxy-ketone*, b.p. 86°/12 mm. (*Staudinger*, *Ruzicka*, Helv. **7**, 377). An isomer has been isolated from crude acetic acid from wood: **1-methyl-Δ^1-cyclopentene-2-ol-3-one,** yellowish crystals, m.p. 105–106°, m.p. of hydrate 72–76°, *dibenzylidene compound* m.p. 207–208°, *Ph-osazone,* m.p. 138–139°. It gives a deep violet colour with $FeCl_3$ solution and is reduced to the saturated hydroxy-ketone, b.p. 97–98°/23 mm. (*Meyerfeld,* Chem.-Ztg. **36**, 549; *Zincke,* Ann. **264**, 211).

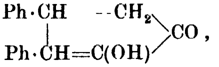
1-Methyl-2-pentadienyl-cyclopentane-4-ol-3-one, *pyrethrolone,* b.p. 111–112°, forms the alcoholic constituent of the ester of chrysanthemic acid (p. 26) which is found in extracts of *Chrysanthemum cinerariifolium* and has insecticidal properties (p. 482) (*Staudinger, Ruzicka,* Helv. **7**, 377, 448). — For other pyrethrolones and Me-cyclopentanolones with different unsaturated side chains see id. ib. pp. 406, 442.

3,4-Diphenyl-Δ^2-cyclopentene-4-ol-1-one, *anhydro-acetone-benzil,*



$$\begin{array}{l} Ph\cdot C{=}{=}CH \diagdown \\ \quad | \qquad\qquad\quad CO \\ Ph\cdot C(OH){-}CH_2 \diagup \end{array}$$

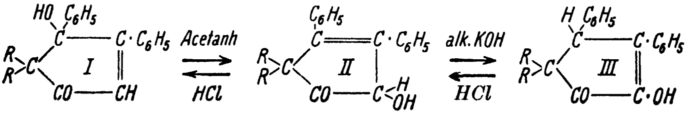
m.p. 149°, is obtained from benzil (vol. III) and acetone. *Vorlander* (Ber. **37**, 1133) has prepared a number of similar cyclopentene keto-alcohols by condensing benzil under pressure with other ketones such as Me-Et-ketone, dibenzyl-ketone etc. By an analogous reaction benzil and laevulinic acid (I, 478) condense to a **diphenyl-cyclopentenolone-acetic acid,** *anhydrobenzil-laevulinic acid* (*Japp, Murray,* J. **71**, 146; *Henderson,* J. **79**, 1256; *Abell,* ib. **53**, 360, 367). An isomeric diphenylcyclopentenolone, m.p. 176°,



$$\begin{array}{l} Ph\cdot CH \;{-}{-}CH_2 \diagdown \\ \quad | \qquad\qquad\qquad CO\,, \\ Ph\cdot CH{=}C(OH) \diagup \end{array}$$

is obtained by the action of conc. H_2SO_4 upon dibenzylidene-acetone. It is oxidised by potassium permanganate to benzil and desyl-acetic acid (vol. III), while both isomers are reduced by hydrogen iodide to 1,2-diphenylcyclopentane (*Vorlander,* Ber. **37**, 1133).

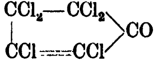
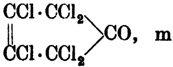
5-Substituted 2- or 4-hydroxy-3,4-diphenyl-Δ^2-cyclopentenones, anhydro-acetone-benzils, are formed by the general method of condensing benzil with aliphatic Me-ketones. These compounds show a characteristic behaviour with acetic anhydride, when they are converted into the acetates of the isomeric 2-hydroxy compound; the following isomeric changes are possible:

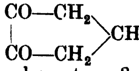
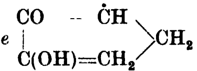


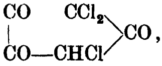
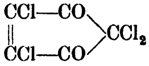
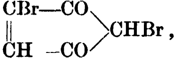
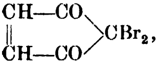
For example, *4-hydroxy-3,4-diphenyl-5,5-dimethyl-Δ^2-cyclopentenone* (I), m.p. 181°, can be converted, via the acetate of II, m.p. 137°, into the isomeric *2-hydroxy-3,4-diphenyl-5,5-dimethyl-Δ^2-cyclopentenone* (III), m.p. 158° (*Japp,* J. **47**, 33; *Gray,* ib. **95**, 2131; *Burton,* Chem. and Ind. **51**, 98; J. **1933**, 720). Reduction of these compounds either with HI and P or by *Clemmensen's* method gives the corresponding cyclopentanes.

2-(3,4,5-Trihydroxy-phenyl)-$\Delta^{2,4}$-cyclopentadiene-1-one-5-ol, *purpurogallin,* is found as the glucoside *dryophanthin,* see p. 425.

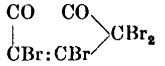
2,3,4,5-Tetraphenyl-Δ^2-cyclopentene-4-ol-1-one, m.p. 210°, is prepared from benzil and dibenzyl ketone with alcoholic potash at ordinary temperature. Elimination of water by means of H_2SO_4 and glacial acetic acid gives *tetraphenyl-$\Delta^{2,4}$-cyclopentadiene-1-one,* dark red crystals melting at 217–218° (*Dilthey,* J. pr. **128**, 139; **139**, 10; **141**, 331). This ketone has been used for diene synthesis (*Allen,* Canad. J. Res. **11**, 171).

Hexachloro-cyclopentenones,  $\begin{array}{l} CCl_2{-}CCl_2\diagdown \\ | \qquad\qquad CO \\ CCl{=}{=}CCl\diagup \end{array}$ and  $\begin{array}{l} CCl\cdot CCl_2\diagdown \\ \| \qquad\qquad CO, \\ CCl\cdot CCl_2\diagup \end{array}$ m.ps. 28° and 92°, b.ps. 156°/80 mm. and 148°/75 mm., are prepared by oxidising the corresponding α-hydroxyacids with CrO_3; the acids are obtained from benzene derivatives such as o-aminophenol and pyrocatechin (vol. III) (*Zincke*, Ber. **24**, 926; **25**, 2697). For the action of NH_3 on these ketones see id., Ber. **31**, 221.

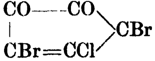
1,2-Cyclopentanedione,  $\left.\begin{array}{l}CO-CH_2\\ |\\ CO-CH_2\end{array}\right>CH_2$, m.p. 56°, is formed by ketonic hydrolysis of 1,2-diketo-cyclopentane-3,5-dicarboxylic ester (p. 69). This diketone has the properties of an acid. It forms salts derived from the tautomeric structure of a *cyclopentenolone*  $\left.\begin{array}{l}CO-\dot{C}H\\ |\\ C(OH)=CH_2\end{array}\right>CH_2$ and it reacts with acetyl chloride, benzoyl chloride and phenyl isocyanate (*Dieckmann*, Ber. **35**, 3201).

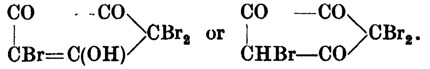
Cyclopentanedione reacts readily with chlorine to form **3-chloro-1,2-cyclopentanedione,** m.p. 139°. *Chlorinated 1,2-cyclopentanediones* can be obtained, like the chlorinated cyclopentenones (above), from benzene derivatives such as phenol and chloranilic acid (*Hantzsch*, Ber. **22**, 1246, 1264; *Heller*, J. pr. **129**, 211). Potassium chloranilate is converted by chlorine and water into **trichloro-cyclopentane-trione**  $\left.\begin{array}{l}CO\quad CCl_2\\ |\\ CO-CHCl\end{array}\right>CO$, m.p. 125°. Resorcinol yields **tetrachloro-cyclopentenedione,**  $\left.\begin{array}{l}CCl-CO\\ \|\\ CCl-CO\end{array}\right>CCl_2$, m.p. 75°, b.p. 148°/27 mm. The primary product of the reaction in these cases is frequently a chlorinated keto-acid; resorcinol, e.g., is converted into perchloro-acetyl-crotonic acid, $CCl_3\cdot CO\cdot CCl:CCl\cdot CCl_2\cdot COOH$. The ring closure to give a ketocyclopentane is then brought about by hot conc. sulphuric acid (*Zincke*, Ber. **24**, 916; **25**, 2225; **26**, 513; *Landolt*, ib. **25**, 848). A similar reaction has been carried out with β,δ-dibromo-laevulinic acid, $CH_2Br\cdot CO\cdot CHBr\cdot CH_2\text{-}COOH$ which is obtained by brominating laevulinic acid; it is converted (*Wolff*, Ann. **294**, 183) by fuming sulphuric acid into two **dibromo-cyclopentenediones**  $\left.\begin{array}{l}CBr-CO\\ \|\\ CH-CO\end{array}\right>CHBr$, m.p. 99°, and  $\left.\begin{array}{l}CH-CO\\ \|\\ CH-CO\end{array}\right>CBr_2$, m.p. 137°.

2,2,3,4-Tetrabromo-Δ³-cyclopentene-1,5-dione, *xanthogallol,*



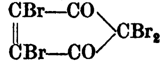
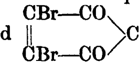
$$\left.\begin{array}{l}CO\quad CO\\ |\\ CBr:CBr\end{array}\right>CBr_2$$

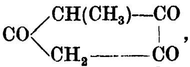
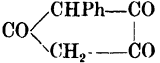
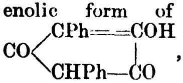
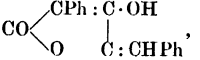
crystallises in orange-coloured plates melting at 121°. It is obtained from pyrogallol (vol. III) by the action of bromine. The bromine atom in the 3-position is highly reactive and can easily be replaced by Cl, basic residues, OH etc. *Chloro-xanthogallol,*  $\left.\begin{array}{l}CO-CO\\ |\\ CBr=CCl\end{array}\right>CBr$, m.p. 99–110°. *Anilido-xanthogallol,* m.p. about 195°. *Xanthogallolic acid,* m.p. 137° decomp.,



$$\left.\begin{array}{l}CO-CO\\ |\\ CBr=C(OH)\end{array}\right>CBr_2 \text{ or } \left.\begin{array}{l}CO-CO\\ |\\ CHBr-CO\end{array}\right>CBr_2.$$

The enolic form of this compound gives a *Me-ether,* m.p. 109–111°, and an *acetate,* m.p. 125–129° (*Moore*, Am. **39**, 980; *Hantzsch*, Ann. **488**, 205).

2,2,4,5-Tetrabromo-Δ⁴-cyclopentene-1,3-dione,  $\left.\begin{array}{l}CBr-CO\\ \|\\ CBr-CO\end{array}\right>CBr_2$, m.p. 143–144°, isomeric with xanthogallol, is formed by the action of an excess of bromine on 4- or 5-nitro-o-acetaminophenol, presumably through 5,6-di- or 3,5,6-tribromo-2-acetaminoquinone as an intermediate. With aniline it gives a compound  $\begin{array}{l}\text{CBr—CO}\\ \|\\ \text{CBr—CO}\end{array}\!\!>\text{C(NHC}_6\text{H}_5)_2$, m.p. 261° decomp., while with NaOBr bromoform and symm. dibromo-maleic acid are formed (*Heller*, J. pr. **129**, 233).

2-Methyl-cyclopentane-1,3,4-trione,  $\text{CO}\!<\!\begin{array}{l}\text{CH(CH}_3\text{)—CO}\\ \qquad\qquad\quad |\\ \text{CH}_2\text{———CO}\end{array}$, m.p. 118°, has been prepared from oxalic ester and Me-Et-ketone by *Diels* (Ber. **39**, 1336) according to method 4b, p. 19. Me-benzyl-ketone gives similarly **phenyl-cyclopentane-trione,**  $\text{CO}\!<\!\begin{array}{l}\text{CHPh—CO}\\ \qquad\quad |\\ \text{CH}_2\text{——CO}\end{array}$ yellow needles m.p. 167° (*Wislicenus*, Ann. **436**, 101). Dibenzylketone gives the asymm. mono-enolic form of **diphenyl-cyclopentane-trione,** *oxalyl-dibenzylketone*,  $\text{CO}\!<\!\begin{array}{l}\text{CPh}=\!=\text{COH}\\ \qquad\quad |\\ \text{CHPh—CO}\end{array}$, m.p. 193°. This compound, when heated, undergoes a rearrangement into *pulvinone* (pulvinolactone, *iso-oxalyl-dibenzylketone*), m.p. 248–249°,  $\text{CO}\!<\!\begin{array}{l}\text{CPh:C·OH}\\ \qquad |\\ \text{O}\quad\text{C:CHPh}\end{array}$, the lactone of a straight chain acid (*Claisen*, Ber. **27**, 1353; Ann. **284**, 295).

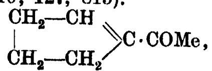
Tri-thiocyclopentanone $(\text{C}_5\text{H}_8\text{S})_3$, m.p. 172°, is formed by the action of HCl and H_2S on cyclopentanone in EtOH.

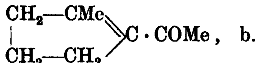
Triquinoyl, C_6O_6, a compound obtained by oxidation of hexahydroxy-benzene $\text{C}_6\text{H}_6\text{O}_6$ or of potassium-carbon-monoxide, undergoes a benzilic acid rearrangement with alkali giving **1,2-dihydroxy-Δ^1-cyclopentene-3,4,5-trione,** *croconic acid*, $\text{C}_5\text{H}_2\text{O}_5$. This can be oxidised to **pentaketo-cyclopentane,** *leuconic acid*, C_5O_5. The reduction product of triquinoyl, *rhodizonic acid*, $\text{C}_6\text{H}_2\text{O}_6$, gives **1,2,4-trihydroxy-Δ^1-cyclopentene-3,5-dione,** *croconic acid hydride*, $\text{C}_5\text{H}_4\text{O}_5$ (cf. ring transitions p. 13) (*Nietzki*, Ber. **18**, 499, 1833; **19**, 293; **20**, 1617; **23**, 3136).

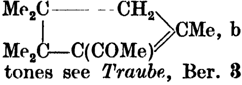
EXOCYCLIC KETONES

Acetylcyclopentane, $\text{C}_5\text{H}_9\text{COCH}_3$, b.p. 160°, *semicarbazone*, m.p. 142–143°, is obtained from cyclopentane with acetyl chloride and AlCl_3 (*Nenitzescu*, Ber. **65**, 810). **1-Methyl-1-acetyl-cyclopentane,** $\text{C}_5\text{H}_8\text{(Me)(COMe)}$, b.p. 60°/13 mm., *semicarbazone* m.p. 143° (*Meerwein*, Ann. **417**, 257; *Nametkin*, Ber. **57**, 585). **1-Methyl-2-acetylcyclopentane,** b.p. 168°, is obtained from the corrresponding carboxylic acid (p. 69). A stable form b.p. 168°/763 mm., *semicarbazone*, m.p. 167°, is obtained from cyclohexane with acetyl chloride and AlCl_3; the ring contracts, and bicyclo-(0,1,3)-hexane is probably an intermediate. A labile form, *semicarbazone*, m.p. 166·5–167° (mixed with the stable form, m.p. 157–158°), is prepared by hydrogenating the unsaturated ketone (cf. below) (*Nenitzescu*, Ann. **491**, 189; Ber. **65**, 808, 1451; **66**, 969; *Zelinsky*, Ann. **508**, 115; *Hopff*, Ber. **65**, 482). **1-Phenyl-3-acetyl-cyclopentane,** b.p. 163–165°/16 mm., is obtained from cyclopentene, acetyl chloride and benzene with AlCl_3 (*Nenitzescu*, Ann. **519**, 267).

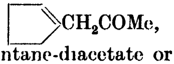
Cyclopentylacetone, b.p. 179°, *semicarbazone*, m.p. 171–171·5°, is the product of the catalytic reduction of Δ^1-cyclopentenylacetone (see below) (*Kon, Linstead*, J. **119**, 810; **127**, 815).

Acetyl-Δ^1-cyclopentene,  $\begin{array}{l}\text{CH}_2\text{—CH}\\ |\\ \text{CH}_2\text{—CH}_2\end{array}\!\!>\text{C·COMe}$, b.p. 173–174°, resembles benzaldehyde in odour. Its *oxime*, m.p. 91°, is formed by loss of HCl from the nitrosochloride of ethylidene-cyclopentane.

1-Methyl-2-acetyl-Δ^1-cyclopentene,  $\begin{array}{l}CH_2{-}CMe\diagdown\\ |\qquad\qquad\quad C\cdot COMe\\ CH_2{-}CH_2\diagup\end{array}$, b.p. 185°/744 mm., *semicarbazone* m.p. 221°, *oxime*, m.p. 85°, has been prepared by the following methods: from 2,7-diketo-octane with NaOEt, from Me-cyclopentane or Me-cyclopentene by acetylation in the presence of $AlCl_3$ (*Zelinsky*, Ann. **508**, 115), and by ring contraction from cyclohexane with acetyl chloride and moist $AlCl_3$ (*Hopff*, Ber. **65**, 483; *Nenitzescu*, ib. **65**, 811, 1452; **66**, 969; Ann. **510**, 269). It gives γ-acetyl-butyric acid when oxidised by $KMnO_4$.

The reduction of mesityl oxide (I 273; *Harries*, Ann. **296**, 295) gives rise, presumably through a 1,6-diketone, to **Pentamethyl-acetyl-cyclopentene,**  $\begin{array}{l}Me_2C{-}{-}{-}CH_2\diagdown\\ |\qquad\qquad\qquad\quad CMe\\ Me_2C{-}C(COMe)\diagup\end{array}$, b.p. 210–230°. For similar ring closures of 1,6 diketones see *Traube*, Ber. **31**, 2938; *Blaise*, C. r. **148**, 852.

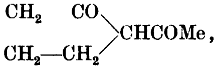
The action of conc. H_2SO_4 on camphor nitrimine (p. 287) gives **1-acetyl-3-isopropyl-Δ^1-cyclopentene,** *isocamphor*, $C_{10}H_{16}O$, b.p. 211°, *semicarbazone* m.p. 164°. The constitution of the compound is shown by its oxidation to α-isopropyl-glutaric acid (*Wallach*, Ann. **379**, 220; **392**, 60).

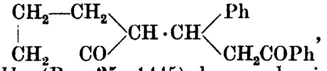
Δ^1-Cyclopentenyl-acetone,  $C_5H_7{\cdot}CH_2COMe$, b.p. 181–184°, is prepared by distilling calcium cyclopentane-diacetate or by treating the chlorides of cyclopentylidene-acetic or Δ^1-cyclopentenyl-acetic acids with MeZnI. Two *semicarbazones* are formed, which can be separated by means of MeOH. The more soluble one melts at 138°, the less soluble at 189° (*Kon, Linstead*, J. **119**, 810; **127**, 815; *v. Braun*, Ber. **67**, 278).

2-Methyl-Δ^1-cyclopentenyl-acetone and **2-Methyl-cyclopentylidene-acetone,** b.ps. 108°/27 mm. and 82°/17 mm., are obtained from 2-Me-Δ^1-cyclopentenyl-acetyl chloride and 2-Me-cyclopentylidene-acetyl chloride resp. with MeZnI (*Bardhan*, J. **1928**, 2603).

ω-Δ^1-Cyclopentenyl-acetophenone, $C_5H_7{\cdot}CH_2{\cdot}COPh$, b.p. 163–165°/16 mm., is prepared from cyclopentenyl-acetyl or cyclopentylidene-acetyl chloride with PhMgBr (*Farrow, Kon*, J. **1926**, 2123).

1-Benzoyl-2-phenyl-Δ^1- and **-Δ^2-cyclopentenes** result from the decomposition of 1,4-dibenzoyl-butane at 300° (*Skraup* et al., Ber. **58**, 2488).

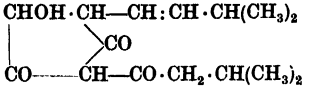
2-Acetyl-cyclopentanone-1,  $\begin{array}{l}CH_2\quad CO\diagdown\\ \qquad\qquad\qquad CHCOMe\\ CH_2{-}CH_2\diagup\end{array}$, b.p. 75°/8 mm., is prepared from ε-keto-oenanthic acid by method 4c, p. 19. The ring easily opens again when the compound is heated with NaOEt (*Blaise*, C. r. **148**, 1401).

The **diketone**  $\begin{array}{l}CH_2{-}CH_2\diagdown\qquad\quad\diagup Ph\\ |\qquad\qquad\quad CH{\cdot}CH\\ CH_2\quad CO\diagup\qquad\quad\diagdown CH_2COPh\end{array}$, m.p. 149–151°, has been obtained by *Stobbe* (Ber. **35**, 1445) by condensing cyclopentanone with benzylidene-acetophenone in EtOH with NaOH.

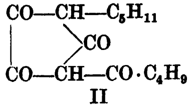
2-Acetyl-3-methyl-cyclopentanone-1, b.p. 89–90°/12 mm. is obtained from γ-Me-δ-acetyl-valeric ester by internal condensation, in accordance with method 4a, p. 19 (*Godchot*, C. r. **176**, 1151).

5-Nitro-2,3-diacetyl-cyclopentadiene, $C_9H_9O_4N$, pale yellow crystals, m.p. 195° decomp., is the chief product of the condensation of acetonylacetone and nitro-malonic aldehyde, while acetonyl-nitrophenol is a by-product (*Hale*, Ber. **45**, 1596).

3-Isoamenyl-1-isovaleryl-4-hydroxycyclopentane-2,5-dione, *humulinic acid* (I), m.p. 93°, and **3-Isoamyl-1-isovaleryl-cyclopentane-2,4,5-trione,** *isohumulinic acid* (II), yellow needles, m.p. 143°, are both degradation products of the hexacarbocyclic ***humulone*** from lupulin (p. 400 and *Wieland*, Ber. **58**, 2012).



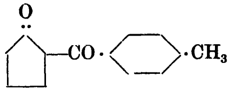
I (or an enolic form of this)



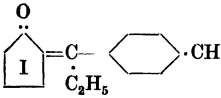
II

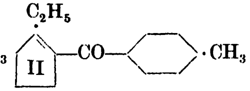
2-Benzoyl-cyclopentanone-1, yellow leaflets, m.p. 41–42°, b.p. 137°/3 mm., *semicarbazone* m.p. 223°, is prepared from δ-benzoyl-valeric ester by internal condensation by means of $NaNH_2$; it is a β-diketone, and since it gives a blood-red colour with $FeCl_3$ it is at least partly enolised in solution (*Meerwein*, Ann. **405**, 129; *Grateau*, C. r. **191**, 947).

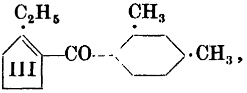
A case of steric hindrance where the aromatic nucleus is substituted is of particular interest. While in **2-p-methylbenzoyl-cyclopentanone-1**



both carbonyl groups are capable of reacting with *Grignard* compounds, e.g. EtMgBr, to form the two unsaturated ketones I and II by loss of water,



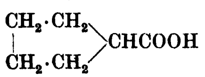


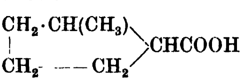


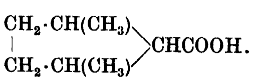
2-o, p-dimethylbenzoyl-cyclopentanone-1 can only be converted into the pentenone III, the *Grignard* reaction with the other carbonyl being prevented by the presence of a Me-group in the o-position. The constitution of compound (I) is proved by its hydrolysis to cyclopentanone and p-methyl-propiophenone, as well as by its oxidation to glutaric acid and p-methyl-propiophenone, while that of the compounds II and III follows from their oxidation to γ-propionyl-butyric and p-toluic acids, and γ-propionyl-butyric and 2,4-dimethylbenzoic acids respectively (*Grateau*, C. r. **196**, 1619).

CARBOXYLIC ACIDS

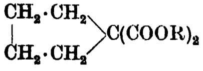
Cyclopentane-carboxylic acid, m.p. 4–5°, b.p. 215°, has an unpleasant odour. **2-Methyl-cyclopentane-carboxylic acid,** b.p. 219°. **2,5-Dimethyl-cyclopentane-carboxylic acid** is known in three stereoisomeric forms, m.ps. 75–77°, 26–30° and 49–50°.

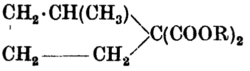


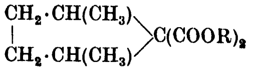




These acids have been prepared from cyclic malonic esters,







which are derived from the corresponding alkylene dibromides by method 5, p. 19 (*Haworth*, Ber. **26**, 2246; *Stauss*, ib. **27**, 1228; *Wislicenus*, ib. **34**, 2565). Cyclopentanecarboxylic acid is also obtained by treating chloro-cyclopentane with Mg and CO_2, from the corresponding α-hydroxy acid or the unsaturated acid, by the action of NaOBr on acetyl-cyclopentane, and by ring contraction of chloro-cyclohexanone, m.p. 23–24°, with the aid of KOH in EtOH (*Favorski*, C. 1915 I 984). The 2-methyl derivative has been obtained from the corresponding α-acetylcarboxylic acid and from 2-methyl-1-acetyl-cyclopentane (p. 60) (*Hopff*, Ber. **65**, 482; *Nenitzescu*, ib. **65**, 811.

1-Methyl-cyclopentane-1-carboxylic acid, b.p. 219°, is prepared from 1-methyl-cyclopentyl-Mg-halide with CO_2 (*Tchitchibabin*, C. 1913 I 2028). **3-Methyl-cyclopentane-1-carboxylic acid,** b.p. 116°/15 mm., $[\alpha]_D$ —5·89°, is formed by the action of Mg and CO_2 on 3-Me-cyclopentyl iodide (*Zelinsky*, Ber. **35**, 2690) or by that of alcoholic KOH on chloro-methyl-cyclohexane of m.p. 55–56° (*Favorski*, C. 1915 I 984). It is isomeric with cyclopentane-acetic acid (cf. below), $C_5H_9CH_2COOH$, which *Baeyer* has prepared (Ber. **29**, 1907) by decarboxylating the condensation product of iodo-cyclopentane and Na-malonic ester. **1-Phenyl-cyclopentane-1-carboxylic acid,** m.p. 155–157°, and **1-phenyl-3-methyl-cyclopentane-1-carboxylic acid,** m.p. 124° are obtained by the mild oxidation of the corresponding aldehydes (*Lévy*, C. r. **187**, 45).

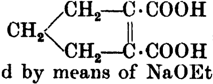
Two modifications of **cyclopentane-1,2-dicarboxylic acid** are known. The cis form, m.p.134–135° (*Wassermann*, Helv. **13**, 207, 223), which forms an anhydride, is obtained by method 6, p. 20, or by heating *cyclopentane-1,1-2,2-tetracarboxylic acid*, which is obtained from trimethylene bromide, sodium and malonic ester (*Perkin*, J. **65**, 580; *Kotz*, J. pr. **64**, 394). The trans acid, m.p. 182°, can be resolved by means of the brucine salt into the *d*-acid, m.p. 181°, $[\alpha]_D$ $+87{\cdot}6^\circ$, and the *l*-acid, m.p. 180–181°, $[\alpha]_D$ $-85{\cdot}9^\circ$. At 300° it undergoes rearrangement to form the cis-anhydride (*Perkin*, J. **65**, 588; *Goldsworthy, Perkin*, **105**, 2639, 2664).

1,1,3,3-Cyclopentane-tetracarboxylic acid, which is obtained similarly, on heating gives cis-**Cyclopentane-1,3-dicarboxylic acid,** *nor-camphoric acid*, m.p. 121°, *anhydride* m.p. 161°. This is also formed by ozonisation of 3,6-endo-methylene-Δ^1-tetrahydrophthalic anhydride (*Diels*, Ann. **478**, 152). It undergoes partial rearrangement into the trans acid, m.p. 88°, when heated with hydrogen chloride (*Pospischill*, Ber. **31**, 1950). *Perkin* and *Scarborough* have resolved the latter into optical antimers (J. **119**, 1400). *Camphoric acid*, which is a 1,2,2-trimethyl-cyclopentane-1,3-dicarboxylic acid, is described in the section dealing with camphor (p. 304).

Cyclopentane-1,2,3-tricarboxylic acid, $C_5H_7(COOH)_3$, cis m.p. 184°, trans m.p. 169–170°, is obtained from α,α′-dibromo-adipic ester and Na-malonic ester or Na-cyanacetic ester. The primary product of the condensation, the 1,2,2,3-tetracarboxylic ester, is first hydrolysed and then the tetracarboxylic acid is heated (*Perkin* et al., J. **119**, 1400; **125**, 1492).

Cyclopentane-1,2,4-tricarboxylic acid is obtained from **1,1,2,2,4,4-cyclopentane-hexacarboxylic ester** which is prepared according to method 6, p. 20, by treating the di-sodium salt of pentane-1,3,5-hexacarboxylic ester with bromine. Trans-cyclopentane-1,2,4-tricarboxylic acid, m.p. 129°, is obtained from the cis acid by heating with conc. HCl (*Perkin* et al., J. **77**, 294; **105**, 2639).

Δ^1-Cyclopentene-carboxylic acid, $C_5H_7{\cdot}COOH$, m.p. 121°, was prepared by *Baeyer* from the corresponding aldehyde (p. 54) by oxidation with Ag_2O (*Urion*, Ann. chim. (11) **1**, 5) or from cyclopentanone-cyanhydrin through the unsaturated nitrile (*Cook, Linstead*, J. **1934**, 956). $KMnO_4$ oxidises it to glutaric acid.

Δ^1-Cyclopentene-1,2-dicarboxylic acid, 

$$CH_2\left\langle\begin{array}{l}CH_2-C\cdot COOH\\ \qquad\quad \| \\ CH_2-C\cdot COOH\end{array}\right.$$

, m.p. 178°, is obtained from α,α′-dibromo-pimelic acid by means of NaOEt (p. 19), and from 1,2-dibromo-cyclopentane-1,2-dicarboxylic acid, which is prepared by brominating cyclopentane-dicarboxylic acid, by treatment with EtOH and KI. It readily adds on 2 Br and is converted into adipic acid by fusion with potash (*Willstatter*, Ber. **28**, 655). **Δ^1-Cyclopentene-1,3-dicarboxylic acid,** m.p. 150·5°, is prepared from 1,1,4,4-butane-tetracarboxylic ester by ring closure, reduction and dehydration (*Nandi*, J. Indian Ch. Soc. **11**, 277).

Bis-cyclopentadiene-carboxylic acid has been mentioned (p. 50) in connection with cyclopentadiene.

CYCLOPENTANE FATTY ACIDS

Cyclopentyl-acetic acid, $C_5H_9CH_2COOH$, b.p. 226–230°, *amide* m.p. 145°, was prepared by *Wallach* (Ann. **353**, 304) by treating cyclopentanol-acetic ester with HBr and reducing the resulting product, while *W. Huckel* (J. pr. **142**, 205) has obtained it, through cyclopentenyl-acetic ester, from cyclopentanone and bromo-acetic ester.

α-Cyclopentyl-propionic acid, $CH_3CH(C_5H_9)COOH$, b.p. 238·5–241°, has been prepared from cyclopentyl bromide and methyl-malonic ester with Na. *Methyl-cyclopentyl-malonic acid,* m.p. 150–151°, is first obtained and loses CO_2 at 189° (*Tchitchibabin,* C. 1933 II 3409).

Naphthenic Acids[1]. The petroleum from many sources, e.g. that from the Caucasian region, Rumania, North Germany, California, and Japan, is mainly a mixture of hydrocarbons as yet incompletely known: cycloparaffins (the so-called naphthenes) are characteristic constituents and are accompanied by relatively small amounts of **naphthenic acids.** These acids are probably the result of a secondary process during the refining process, in which atmospheric oxygen is involved. The investigation of these acids is of importance in the problem of the constitution of the petroleum hydrocarbons. Preliminary experiments have shown that heating under pressure (cracking) and the "berginisation" of petroleum can also throw light on the nature of the hydrocarbons contained therein (*Ipatiev,* Ber. **63,** 156; *Orlov,* Ber. **63,** 2179).

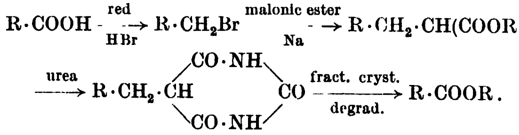
Painstaking investigations have shown the low-boiling fractions of these acids are mainly composed of two *paraffin-carboxylic acids,* $C_6H_{12}O_2$ and $C_7H_{14}O_2$. The middle fractions consist of saturated monocyclic acids of the general formula $C_nH_{2n-2}O_2$, which have been found to be *alkylated carboxylic acids of the cyclopentane series* up to $C_{12}H_{22}O_2$ and have been termed "naphthenic acids". It is difficult to isolate them from the mixtures; *Markownikov* (Ann. **307,** 367) was the first to succeed in preparing a pure individual acid The high-boiling fractions contain mainly bicyclic compounds $C_nH_{2n-4}O_2$ ranging from $C_{13}H_{22}O_2$ to $C_{22}H_{40}O_2$.

In crude Rumanian petroleum no low-boiling naphthenic acids are present. They are presumably formed by the oxidation of the hydrocarbons during the distillation process. Galician and Japanese petroleum, which are rich in paraffins, are free from bicyclic compounds, but in addition to monocyclic acids, contain relatively large amounts of paraffin-carboxylic acids (*Tchitchibabin,* C. 1930 II 2854).

There are great difficulties in the way of separating the homologous naphthenic acids, because the differences of boiling points are small, not only for the acids, but also for their esters. The amines, which display much greater differences in boiling points, are more easily fractionated. They are prepared either by the degradation methods of *Hofmann* and *Curtius,* which, however, involve great losses, or, preferably, by the hydrazoic acid method of *K. Schmidt* (*v. Braun,* Ann. **490,** 105).

An improved method of separating such a mixture of amines was worked out by *v. Braun* (Ber. **66,** 1373). It is based on the differential behaviour of their benzoates when subjected to hydrolysis by conc. HCl.

v. Braun succeeded in obtaining individual acids by a somewhat complicated way, which is indicated in the scheme below. The bromides were condensed with malonic ester, and the resulting dicarboxylic esters were combined with urea to give ureides; these were submitted to fractional crystallisation and then oxidised to regenerate the original acid (Ann. **490,** 114):



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[1] General surveys: *Naphtali,* Chemie, Technologie und Analyse der Naphthensauren, Stuttgart 1927. — *v. Braun,* Angew. **41,** 29; **44,** 661; **45,** 231; Ann. **490,** 105.

Constitution of the Acids. — One of the first steps towards the elucidation of the constitution of the naphthenic acids was made by *v. Braun*, when he established the fact that in most of them the carboxyl group was primary, $R\cdot CH_2COOH$, by means of his imidochloride method described on p. 16. *Skraup* introduced the method of superheating carboxylic phenyl-esters (p. 16) in order to diagnose the linkage of the carboxyl group. The phenyl-ester, for instance, of the naphthenic acid $C_{10}H_{18}O_2$, gave by thermal decomposition trimethyl-benzyl-cyclopentane:

$$Me_3C_5H_6\cdot CH_2\cdot COOPh \rightarrow Me_3C_5H_6\cdot CH_2Ph + CO_2.$$

The acid fraction, $C_{10}H_{18}O_2$, b.p. 148–155°/12 mm., of Rumanian illuminating oil was converted into the corresponding cyclic α-bromo-fatty acid, then into the α,β-olefinic acid and by isomerisation into a γ-lactone. This fact indicates the constitution $C_6H_{11}\cdot CH_2\cdot CH_2\cdot CH_2\cdot COOH$ for the original acid.

A practicable way of degrading naphthenic acids is through the amines to olefins, and then by oxidation to cyclic carboxylic acids and finally to ring ketones (p. 17, method 4). From the ketone the length of the original side chain which carries the carboxyl group can be deduced. For instance,

the ketone $C_8H_{14}O$, b.p. 172–174°, *semicarbazone* m.p. 163°, corresponds to the acid $C_{10}H_{18}O_2$;

the ketone $C_{10}H_{18}O$, b.p. 201–204°, *semicarbazone* m.p. 163°, corresponds to the acid $C_{12}H_{22}O_2$;

and the bicyclic ketone $C_{11}H_{18}O$, b.p. 230–238°, *semicarbazone* m.p. 162°, corresponds to the acid $C_{13}H_{22}O_2$; all have been isolated from Californian and Rumanian petroleum.

3,3,4-Trimethyl-cyclopentane-1-acetic acid, $C_{10}H_{18}O_2$, b.p. 144–145°/14 mm., *Et ester* b.p. 113–115°/14 mm., *amide* m.p. 124°, occurs in Rumanian and Californian petroleum. Its constitution was established by degradation through an amine and an olefin to *3,3,4-trimethyl-cyclopentanone-1*, $C_8H_{14}O$, b.p. 172–174°, whose constitution is discussed on p. 56; also by a partial synthesis from the ring ketone by bromo-acetic ester and zinc (*Reformatzky's* reaction) (*v. Braun*, Ber. **66**, 1499).

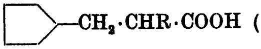
Naphthenic esters all have a very pleasant smell. The ureides are of pharmacological interest as hypnotics. The amines of this series are insecticides (*v. Braun*, Ann. **490**, 100).

A number of α,β-unsaturated acids have been obtained by splitting off water from the 1,1-hydroxyacids described below.

Cyclopentylidene acetic acid, $C_5H_8{:}CHCOOH$, m.p. 64°, b.p. 128–130°/13 mm., undergoes rearrangement when treated with KOH and forms **Δ^1-cyclopentenyl acetic acid,** m.p. 52° (*Goldberg*, J. **1928**, 2343). **Δ^2-Cyclopentenyl acetic acid,** b.p. 94–95°/3 mm., is prepared from Δ^2-cyclopentenyl chloride through cyclopentenyl-malonic ester (*Noller, Adams*, Am. 48, 2444; *Kon, Linstead*, J. **1932**, 2454; French Pat. 728,998). The ester of **2-methyl-cyclopentylidene-1-acetic acid,** $CH_3\cdot C_5H_7{:}CHCOOH$, m.p. 108–109°, is formed from cyclopentanone, Mg and bromoacetic ester. This reaction also gives a hydroxy-ester, which, by removal of water and hydrolysis, is converted into **2-methyl-Δ^1-cyclopentenyl-1-acetic acid,** an oil, b.p. 150°/28 mm. (*Bardhan*, J. **1928**, 2604). **α-Cyclopentylidene-propionic acid,** m.p. 108°. These acids lose CO_2 on dry distillation and give cyclopentane hydrocarbons with semicyclic double-bonds, cf. methylene-cyclopentane, p. 49 (*Wallach*, Ann. **365**, 273; *Speranski*, C. 1902 I 1222).

Higher cyclopentyl fatty acids and Δ^2-cyclopentenyl fatty acids with long or alkyl-substituted side chains have been found to be effective against tuberculosis and leprosy. Some acids of this type, e.g. **hydnocarpic Acid,** $C_{16}H_{28}O_2$, and **chaulmoogric Acid,** $C_{18}H_{32}O_2$, occur as dextrorotatory glycerides in plants belonging to the genera *Hydnocarpus* and *Taraktogenos*. The proof of their constitution is given later in the section Natural Products. Several such fatty acids have been prepared synthetically, and have also been found to be therapeutically effective. They comprise the following types:

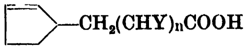
(a) Saturated and unsaturated acids of the general formula



(R = hexyl to dodecyl)

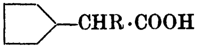
cyclopent(en)yl-α-alkylpropionic acids, from cyclopent(en)yl-Me bromide and Na-alkylmalonic esters (*Noller*, Am. 48, 1080).

(b) Cyclopentenyl fatty acids of the type

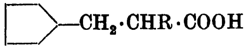


where Y can be H or a monovalent group like Cl, OH etc. They are made from Δ^2-cyclopentenyl-ethyl bromide and Na-compounds of substituted malonic esters (*Adams*, U.S.A. Pat. 1,678,175).

(c) Saturated acids of the type

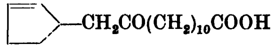


and

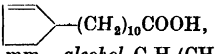


from cyclopentyl-Mg-Br (*Adams* et al., Am. 48, 1080; **50**, 1503). This method furnishes dihydro-derivatives of the natural acids.

(d) The natural acids themselves are obtained as inactive racemic compounds by: ω-bromo- → ω-cyano-undecylic ester + Na-acetoacetic ester + Δ^2-chlorocyclopentene with repeated hydrolysis. The resulting *d,l-λ*-ketochaulmoogric acid

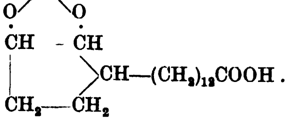


is converted into the inactive acid, m.p. 68·5°, by decomposing its hydrazone with KOH (*Perkins*, Am. 49, 1071).

Hydnocarpic acid, 

m.p. 59·6°, $[\alpha]_D$ + 69·4°. *Et ester* b.p. 143–144°/2 mm., *alcohol* $C_5H_7(CH_2)_{10}CH_2OH$, m.p. 23°, *bromide* b.p. 156–157°/2 mm.

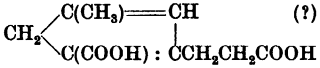
Chaulmoogric acid, *hydnocarpyl-acetic acid,* $C_5H_7\cdot(CH_2)_{12}COOH$, m.p. 68·5–69·5°, $[\alpha]_D$ + 62,4°, *amide* m.p. 104° (natural product), has been obtained synthetically from natural hydnocarpic acid. The bromide of this acid, described above, is caused to react with Na-malonic ester, the resulting ester is hydrolysed and CO_2 is removed from the free acid; m.p. 68°, $[\alpha]_D$ + 61·9°. By adding HBr and then removing it again chaulmoogric acid is converted into an inactive form, m.p. 51–53°. It is oxidised by $KMnO_4$ to *dihydroxychaulmoogric acid* (two isomers) which forms a compound with acetone (*Barrowcliff*, J. 91, 557; *Stanley, Adams*, Am. **51**, 1515):



Both acids, when hydrogenated under pressure in the presence of platinum oxide in EtOH, are rendered inactive with formation of **dihydro-hydnocarpic** and **dihydro-chaulmoogric** acids resp., m.ps. 64–65° and 71–72° (*Shriner, Adams*, Am. **47**, 2727). The sequence of reactions which leads from hydnocarpic acid to chaulmoogric acid may be applied to the latter acid and yields **chaulmoogryl-acetic acid,** $C_5H_7(CH_2)_{14}COOH$, m.p. 72–73°, [α]D + 43° (*Dyke*, Am. **48**, 2393).

Cyclopentane-1-carboxylic-1-acetic acid, m.p. 160°, *anhydride* m.p. 32°, is prepared from cyclopentene-cyano-acetic ester + KCN, the product being hydrolysed with HCl (*Vogel*, J. **1928**, 2010). **Cyclopentane-2-carboxylic-1-acetic acid,** cis m.p. 89°, trans m.p. 66°, from the following acid by reduction (*Cook*, *Linstead*, J. **1934**, 956). **Δ^2-Cyclopentene-2-carboxylic-1-acetic acid,** m.p. 156°, is prepared from succinic dialdehyde, malonic acid and methylamine; 3-methylamino-cyclopentane-2,2-dicarboxylic-1-(malonic-)acetic acid, which is formed first, is subjected to exhaustive methylation (*Mannich*, Arch. Pharm. **270**, 286). **Cyclopentane-1-carboxylic-1-butyric acid,** an oil, see p. 160. **Cyclopentane-1,1-diacetic acid,** m.p. 176–177°, *anhydride* m.p. 68°, results from the corresponding 1,1-dimalonic acid (*Kon*, *Thorpe*, J. **115**, 686). **2-Methyl-cyclopentane-1,1-diacetic acid,** m.p. 90–91°, *anhydride* m.p. 198° (*Bardhan*, J. **1928**, 2591). **3-Methyl-cyclopentane-1,1-diacetic acid,** m.p. 134–135° (*Vogel*, J. **1931**, 907).

The substance obtained by the action of NaOEt on laevulinic ester is probably **methyl-cyclopentadiene-carboxylic-propionic acid,**



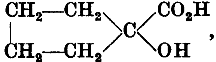
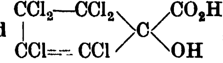
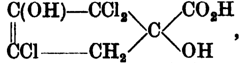
(?) ,

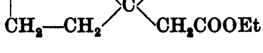
formed by ring closure between two molecules. It melts at 218° with loss of CO_2 to form, first, **methyl-cyclopentadiene-propionic acid,**

$$C_5H_4(CH_3)(CH_2CH_2COOH),$$

m.p. 65°, and then **methyl-ethyl-cyclopentadiene,** $C_5H_4Me\cdot Et$, b.p. 135°. These compounds resemble cyclopentadiene (p. 50) in their general behaviour (*Duden*, Ber. **36**, 944).

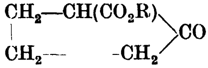
Kon and *Speight* (J. **1926**, 2727) have prepared a number of (*alkyl-*)*cyclopentylidene-malonic esters* by treating (alkyl-) cyclopentanones and malonic ester with acetic anhydride or with $ZnCl_2$ + aniline. *Vogel* (J. **1928**, 2010) has obtained the corresponding *cyano-acetic esters* by an analogous reaction. When these compounds are treated with KOH the semicyclic double bond moves into the ring; reduction yields saturated esters. The free malonic acids lose CO_2 on heating to form acetic acids. *Et Δ^2-cyclopentenyl-malonate,* b.p. 120° from Δ^2-cyclopentenyl chloride and Na-malonic ester (*Noller*, *Adams*, Am. **48**, 2444; French Pat. 728,998; *Kon*, *Linstead*, J. **1932**, 2454). Brit. Pats. 348,140, 349,455 describe alkylsubstituted homologues of these esters.

Hydroxy-carboxylic Acids.—**1,1-Hydroxy-cyclopentane-carboxylic acid,**  , m.p. 103°, prepared by *Mager* (Ann. **275**, 333) from cyclopentanone with HCN and HCl. **1-Methyl-3-amino-cyclopentanecarboxylic acid,** $Me\cdot C_5H_7(NH_2)COOH$, m.p. 299° (*Zelinsky*, Ber. **39**, 1728). **Hexachloro-1-hydroxycyclopentenecarboxylic acid**  , is obtained from the chlorination product of cyclohexene-1,2-dione with sodium carbonate or sodium acetate. When heated, it is transformed into an isomeric acid, and on boiling with water both these acids give perchloro-indone (vol. III) (*Zincke*, Ber. **23**, 824; Ann. **272**, 243). **Trichloro-cyclopentene-dihydroxycarboxylic acid,**  , has been found by *Hantzsch* (Ber. **22**, 2827) among the products of the action of chlorine on phenol in alkaline solution.

1,1-Cyclopentanol-acetic ester,  , b.p. 105–107°/

11 mm., is obtained by condensing cyclopentanone and bromo-acetic ester by means of zinc. By similar reactions **3-Methyl-1,1-cyclopentanol-acetic ester,** $Me\cdot C_5H_7(OH)(CH_2COOEt)$, b.p. 90—92°/11 mm., **1,1-cyclopentanol-α-propionic ester,** $C_5H_8(OH)CHMeCOOEt$, and **1,1-cyclopentanol-α-isobutyric ester,** $C_5H_8(OH)CMe_2COOEt$, b.p. 108–113°/11 mm., are obtained. **1-Methyl-3-isopropylcyclopentane-1-ol-3-carboxylic acid,** m.p. 113–114°, is formed when piperitone (q.v.) is oxidised by O_2 in alkaline EtOH; it is converted, by elimination of water, into the corresponding ring-unsaturated acid, *piperitolenic acid,* m.p. 57–59° (*Treibs,* Ber. **64,** 2545). **2,2,4-Trichloro-Δ^3-cyclopentene-1,3-dihydroxy-1-carboxylic acid,** m.p. 176–177°, is the primary degradation product when phenol is treated with chlorine in alkaline solution. Its methyl ester gives with NH_3 a trichloro-dihydroxypicoline (vol. IV) (*Hoffmann,* Ber. **22,** 1264).

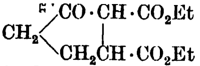
Keto-carboxylic Acids.—**2-Cyclopentanone-carboxylic ester,**



$$\left.\begin{array}{l}CH_2-CH(CO_2R)\\ |\\ CH_2-\!\!-\!\!-\!\!-CH_2\end{array}\right\rangle CO$$

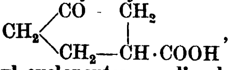
b.p. 117°/26 mm., is prepared from adipic ester by method 4a p. 19. It displays the typical reactions of aceto-acetic ester (I, 471). Though containing only 4% of enol, it is strongly acid and the salts are not decomposed by CO_2, which shows that acidity and enol content are not related (*Dieckmann,* Ber. **55,** 2473). For the keto-enolic equilibrium in different solvents see ib. p. 2470. Ketonic hydrolysis gives cyclopentanone, acid hydrolysis regenerates adipic acid; amyl nitrite + NaOEt convert it into α-oximino-adipic ester. *Haller* (Bull. **39** (1926), 1621) has prepared methyl-derivatives: **1-methyl-2-cyclopentanone- and 1,3-dimethyl-2-cyclopentanone carboxylic esters,** b.ps. 108°/22 mm. and 121°/32 mm., both by means of MeI and NaOEt; **3- and 4-Methyl-2-cyclopentanone carboxylic esters** from α- and β-methyl-adipic esters (*Dieckmann,* Ann. **317,** 27; *Bouveault* and *Locquin,* C. r. **146,** 138; *Haller,* l. c.).

Cyclopentanone-2,3-dicarboxylic ester,



$$CH_2\left\langle\begin{array}{l}CO\cdot CH\cdot CO_2Et\\ \quad\;\; |\\ CH_2CH\cdot CO_2Et\end{array}\right.$$

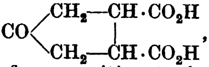
, b.p. 166°/18 mm., was prepared by *Haworth* and *Perkin* (J. **93,** 579) from butane-1,2,4-tricarboxylic ester by method 4a p. 19. When hydrolysed it loses CO_2 and forms **Cyclopentanone-3-carboxylic acid,**



$$CH_2\left\langle\begin{array}{l}CO - CH_2\\ \qquad\; |\\ CH_2-CH\cdot COOH\end{array}\right.$$

, m.p. 65°. *Stobbe* (Ann. **315,** 219) obtained a **phenyl-cyclopentanone-dicarboxylic acid** by the same method from 2-phenyl-1,3,4-butane-tricarboxylic ester.

Cyclopentanone-3,4-dicarboxylic acid,

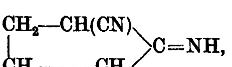


$$CO\left\langle\begin{array}{l}CH_2-CH\cdot CO_2H\\ \qquad\;\; |\\ CH_2-CH\cdot CO_2H\end{array}\right.$$

, m.p. 189°, has been prepared by *Auwers* (Ber. **26,** 373) from aconitic ester by condensing it with Na-malonic ester and degrading the product.

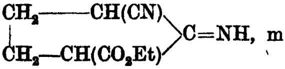
Dimethyl-butane-tricarboxylic ester, when treated with Na and MeI, gives a **trimethyl-cyclopentanone-dicarboxylic ester** which is supposed to contain a grouping of atoms similar to that in *camphoric acid* (*Mahla, Tiemann,* Ber. **33,** 1929). For dimethyl-cyclopentanone polycarboxylic acids see *Toivonen,* C. 1923 I 1357.

1-Imino-2-cyano-cyclopentane,



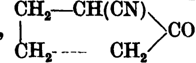
$$\left.\begin{array}{l}CH_2-CH(CN)\\ |\\ CH_2-\!\!-\!\!-CH_2\end{array}\right\rangle C{=}NH$$

, m.p. 147°, is the product of the intramolecular condensation of adipic dinitrile under the action of NaOEt. **2-Imino-3-cyano-cyclopentane-1-carboxylic ester,**

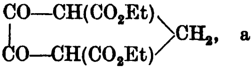


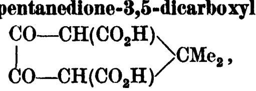
$$\left.\begin{array}{l}CH_2-\!\!-\!\!-CH(CN)\\ |\\ CH_2-CH(CO_2Et)\end{array}\right\rangle C{=}NH$$

, m.p. 119·5°, is obtained by a similar reaction.

by the action of Na-cyano-acetic ester upon 1,1-cyano-cyclopropane-carboxylic ester (p. 29), in which α,α′-dicyano-adipic ester is possibly an intermediate. Treatment with acids converts it first into **3-cyano-2-cyclopentanone-carboxylic ester,** b.p. 172–174°/18 mm., then into **2-cyano-cyclopentanone,** , b.p. 229°, and finally into cyclopentanone (*Best, Thorpe,* J. **95**, 685).

A number of 1,2-diketo-cyclopentanecarboxylic acids have been prepared by condensing oxalic ester with esters of the glutaric series and of other similar acids (method 4b p. 19), e.g.:

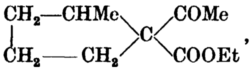
1,2-Cyclopentadione-3,5-dicarboxylic ester, , and derivatives with Me or Ph in the 4-position (*Dieckmann,* Ber. **35**, 3206; *Dickens, Kon, Thorpe,* J. **121**, 1496). Special interest attaches to the ester of **4,4-dimethyl-1,2-cyclopentanedione-3,5-dicarboxylic acid,**



from which *Komppa* (Ann. **368**, 126), by successive reduction of the ketonic groups, has prepared dimethyl-cyclopentane-dicarboxylic acid, *apocamphoric acid* (p. 319).

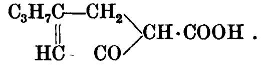
By similar syntheses, **1,2-cyclopentane-dione-3,4,5-tricarboxylic ester** is formed from oxalic and tricarballylic esters, **1,2,4-cyclopentane-trione-3,5-dicarboxylic ester** from oxalic and acetone-carboxylic esters, and **1,2,4-cyclopentane-trione-3-carboxylic ester** from oxalic and β-hydroxy-crotonic esters (*Rimini,* Gazz. **26**, II, 374; *W. Wislicenus,* Ann. **297**, 98; J. pr. **95**, 269; **96**, 174).

2-Methyl-1-acetyl-cyclopentane-1-carboxylic ester,



an exocyclic ketocarboxylic ester, is obtained by method 5, p. 19 (*Colman, Perkin,* Ber. **21**, 742).

4-Isopropyl-Δ³-cyclopentenone-2-carboxylic-1 acid,



The methyl ester is formed when the cyclopropane ring of tanacetone-dicarboxylic acid (p. 32) is disrupted by boiling with NaOMe; MeOH is split off and a five-membered ring is formed (p. 32). The H-atom in the 1-position between CO and COOMe can be substituted by alkyl groups. Hydrogenation gives rise to the saturated ester (*Toivonen,* C. 1928 II 38).

Ketocyclopentane Fatty Acids.—**Cyclopentanone-3-acetic acid,** *semicarbazone* m.p. 199° decomp. Its ester is obtained by ring closure from the adduct of Na-malonic and dihydromuconic esters (*Farmer,* J. **123**, 3324).

1-Acetyl-cyclopentane-1-acetic acid, m.p. 83–84°, is obtained from cyclopentane-1-acetic-ester-1-carboxylic chloride by MeZnI (*Bardhan,* J. **1928**, 2591, 2604).

Cyclopentanone-2,2-diacetic acid, m.p. 112°, is prepared from the hydroxy-spiro compound mentioned on p. 156, by HBr (*Lanfear, Thorpe,* J. **123**, 1683).

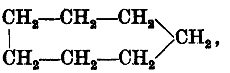
Cyclopentylidene- and **Δ¹-Cyclopentenyl-succinic acids,** m.ps. 205–207° decomp. and 157–159°, *anhydride* of the first, m.p. 53–54°. A mixture of their esters is formed when cyclopentanone and succinic ester are condensed by means of NaOEt; the acids are separated by $CHCl_3$ (*Stobbe,* J. pr. **89**, 29).

Cyclopentylidene-2-one-1,3-dioxalic acid, $C_5H_6O{:}(COCOOH)_2$, m.p. 210° decomp. The Et-ester is formed from cyclopentanone, oxalic ester and NaOEt (*Ruhemann*, J. **101**, 1729).

4. CYCLOHEPTANE GROUP

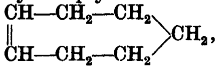
Compounds belonging to this group have acquired an increased interest since it was discovered that they are related to certain alkaloids (cocaine etc.), to terpenes (eucarvone) and to the so-called pseudo-phenylacetic acid. The ease of transition from the hepta-carbocylic structure into the aromatic structure is often remarkable. Syntheses begin in most cases from suberone (*Mager*, Ann. **275**, 356).

Hydrocarbons.—**Cycloheptane,** *suberane, heptamethylene,*

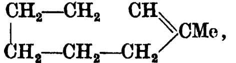


m.p. −12°, b.p. 118—120°, d_4^0 0·8275, is prepared by reducing cycloheptyl bromide or iodide or by hydrogenating cycloheptene (*Seidel*, Helv. **19**, 424). As the heat of combustion is normal the ring must be regarded as strainless. Suberane is converted into pentabromotoluene by $Br_2 + AlBr_3$, and into Me-cyclohexane (hexahydrotoluene) by heating with HI (*Markovnikov*, Ber. **27**, R. 47).

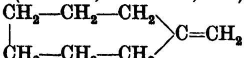
Methyl-cycloheptane, b.p. 133–135°, is obtained from cycloheptanone through methyl-cycloheptene (*Seidel*, l. c.), and **ethyl-cycloheptane,** $C_7H_{13}Et$, b.p. 163°, from $ZnEt_2$ and cycloheptyl bromide.



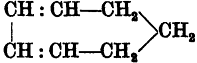
Cycloheptene, *suberene,* , b.p. 115°, has been prepared by *Willstätter* (Ann. **317**, 218) from cycloheptyl iodide and alcoholic KOH, and from cycloheptylamine, which he converted into cycloheptyl-trimethylammonium hydroxide and then distilled. *Ruzicka* (Helv. **9**, 399) obtained it by ring enlargement of cyclohexyl-methylamine with nitrous acid, while *Rosanov* (C. 1924 I 2426; 1930 II 229) heated methylene-cyclohexane (p. 94) or cycloheptanol with anhydrous oxalic acid. For the latter, β-naphthalene-sulphonic acid can be substituted (*Seidel*, l. c.). It unites with bromine to form an unstable dibromide. For the addition of phenyl azide to cycloheptene v. *Alder*, Ann. **501**, 8.



Δ¹-Methyl-cycloheptene, , b.p. 138°, is prepared from Me-cycloheptanol by heating with $KHSO_4$. It is oxidised by $KMnO_4$ to ε-acetyl-caproic acid. *Nitrosochloride* m.p. 106° (*Wallach*, Ann. **345**, 139).

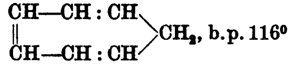


An isomeric hydrocarbon, **Methylene-cycloheptane,** b.p. 139°, has been obtained by *Rosanov* (C. 1930 II 229) by distilling suberene-acetic acid or by treating cycloheptyl carbinol with oxalic acid. *Nitrosochloride* m.p. 81°. Oxidation with $KMnO_4$ gives first the *glycol* $(C_6H_{12}){:}C(OH)CH_2OH$, m.p. 50°, and then hydroxy-suberane-carboxylic acid (p. 74) and suberone (*Wallach*, Ann. **345**, 146).



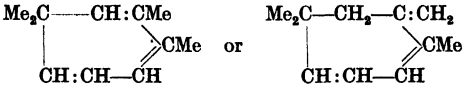
Δ¹,³-Cycloheptadiene, *hydrotropilidene,* , b.p. 121°, is a distillation product of the quaternary ammonium bases which are obtained by the exhaustive methylation of various amino-cycloheptenes (see below); some of these are obtained synthetically, and others are degradation products of tropine. The compound adds on bromine to form an oily 1,4-dibromide. This, when heated with quinoline, splits off 2HBr and gives:

Cycloheptatriene, *tropilidene,*



b.p. 116°, the dibromide of which is transformed into benzyl bromide by heating with HBr to 100° (*Willstätter*, Ann. **317**, 204; Ber. **31**, 1544).

A **tetramethyl-cycloheptatriene,**



b.p. 67–68°/11 mm., is prepared from cucarvone and MeMgI, the corresponding tertiary alcohol being an intermediate (*Rupe*, Ber. **44**, 2702).

Cycloheptine, C_7H_{10}, b.p. 120–126°, can be obtained from 1,2-dibromocycloheptane with alcoholic KOH (*Markovnikov*, J. pr. **49**, 430; Ann. **327**, 67; *Favorsky*, Ann. **390**, 122).

Alcohols.—**Cycloheptanol,** *suberyl alcohol,* $C_7H_{13}OH$, b.p. 184°, has been obtained by *Godchot* (C. r. **171**, 1378), together with *suberyl pinacol,* by reducing suberone with Na and EtOH, or by hydrogenating it catalytically. It is converted into hexahydrotoluene by reduction with HI (*Markovnikov*, Ber. **30**, 1216). *Chloride* b.p. 174°, *bromide* b.p. 101°/40 mm., *iodide* d_{15} 1·572, *phenylurethane* m.p. 85°. **Cycloheptylamine,** $C_7H_{13}NH_2$, b.p. 169°, is obtained from suberone oxime by reduction, or from suberane-carboxylic amide with KOBr (*Markovnikov*, Ber. **26**, R. 813; *Willstatter*, Ann. **317**, 219).

1,1-Methyl-cycloheptanol, (C_7H_{12}):C(OH)Me, b.p. 183–185°, is obtained from suberone and MgMeI.

2-Methyl-cycloheptanol-1, cis b.p. 191°, trans b.p. 194°, from the ketone by reduction with H + Pt in AcOH or with Na + EtOH. *Phenylurethanes* m.ps. 40–41° and 59–60°. *Mono-phthalates* m.ps. 86° and 98°. **2,2-Dimethyl-cycloheptanol-1,** b.p. 196–197°, is obtained similarly from the corresponding ketone by reduction with Na and moist Et_2O; *phenylurethane* m.p. 97° (*Godchot*, Bull. **13** (1913), 12; C. r. **190**, 642; *Meerwein*, Ann. **396**, 200). When this compound is heated with $ZnCl_2$ water is split off and the ring contracts; Δ^1-isopropyl-cyclohexene and probably 2,2-Me_2-Δ^1-cycloheptene are formed (*Meerwein*, J. pr. **104**, 289).

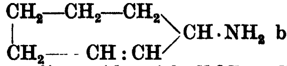
Cycloheptane-1,2-diol, cis m.p. 46°, from cycloheptene with $KMnO_4$; trans. m.p. 63°, from cycloheptene oxide with boiling dilute HCl (*Böeseken*, Rec. **40**, 529). **Cycloheptene oxide,** b.p. 161°, is prepared from cycloheptene with perbenzoic acid. It gives with NH_4OH **2-amino-cycloheptanol,** m.p. 72–78°, *hydrochloride* m.p. 115–116° (*Godchot*, C. r. **184**, 208; **196**, 1680).

Cycloheptenyl-ethyl ether, $C_7H_{11}OEt$, b.p. 174°, is made from cycloheptene dibromide (p. 70) with alcoholic potash.

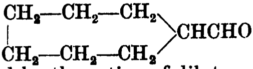
Cycloheptyl carbinol, $C_7H_{13}CH_2OH$, b.p. 80–90°/15 mm., is obtained from bromide with Mg and trioxymethylene. *Bromide* b.p. 81–82°/15 mm. (*v. Braun* et al., Ber. **59**, 1081).

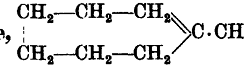
Cycloheptyl-methylamine, $C_7H_{13}\cdot CH_2NH_2$, b.p. 193–195°, is prepared from the amide of cycloheptane-acetic acid with bromine and alkali. Nitrous acid acts on this compound to give cyclo-octanol (p. 76) together with cycloheptyl carbinol (*Wallach*, Ann. **353**, 327).

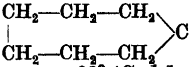
Δ^2-Aminocycloheptene,



b.p. 166°, is obtained from Δ^2-cycloheptene-carboxylic amide with KOBr. When methylated it gives **Δ^2-dimethylamino-cycloheptene,** $C_7H_{11}NMe_2$, b.p. 188°, which is also obtained from cycloheptene dibromide (cf. above) with $NHMe_2$. It is isomeric with the two *methyl-tropanes* which *Willstätter* isolated from the degradation products of the alkaloid tropine and which he assumed to be Δ^3- and Δ^4-*Me$_2$-amino-cycloheptenes* (Ann. **317**, 204 et seq.). **Δ^4-Dimethylamino-cycloheptene,** $C_7H_{11}NMe_2$, b.p. 188°, is prepared by reducing the (bromo-) tropane methohalides (vol. IV).

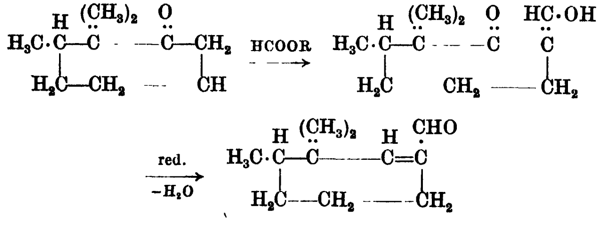
Aldehydes.—Cycloheptane aldehyde,  an oil which smells like benzaldehyde, is formed by the action of dilute sulphuric acid on the glycol of methylene-cycloheptane (p. 70) (*Wallach,* Ann. **345**, 149).

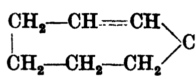
Δ^1-Cycloheptenyl aldehyde,  *semicarbazone,* m.p. 204°, also has a marked odour of benzaldehyde. It has been prepared from the nitrosochloride of methylene-cycloheptane by removal of HCl and treatment of the resulting oxime with acid. It is oxidised by silver oxide to cycloheptene-carboxylic acid (see below).

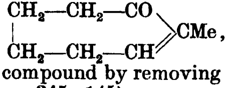
Ketones.—Cycloheptanone, *suberone,*  b.p. 179°, *semicarbazone,* m.p. 164°; *α,α'-dibromide,* m.p. 68° (*Godchot,* C. r. **174**, 618), has an odour of peppermint and is obtained from 1,4-dibromobutane and acetone-dicarboxylic ester (*v. Braun,* Ber. **46**, 1792), by distilling calcium suberate, by distilling free suberic acid with catalysts such as iron filings + BaO (Germ. Pat. 356,622; *Vogel,* J. **1929**, 721), or, in good yield, from the corresponding dinitrile by *Ziegler's* method (cf. method 8 p. 21, and large rings p. 79). It is also formed, together with cyclo-octanone, by ring enlargement from cyclohexanone (p. 109) by treatment with diazo-methane (*Mosettig,* Am. **52**, 3456). It is oxidised to pimelic acid. Like cyclohexanone (p. 109) it condenses with benzaldehyde: *dibenzylidene compound* m.p. 108° (*Einhorn,* Ber. **29**, 1600). *Suberone oxime,* $C_7H_{12}(NOH)$, m.p. 23°, b.p. 230°, undergoes rearrangement into ζ-heptalactam (I 451) when treated with conc. sulphuric acid.

Alkylated cycloheptanones are obtained from suberic acids alkylated in α- or β-position. **2-Methyl-cycloheptanone-1,** b.p. 185–186°/760 mm., gives an oily oxime. **2,2-Dimethyl-cycloheptanone-1,** b.p. 191–192°/770 mm., *oxime* m.p. 83°, is obtained from suberone with MeI and $NaNH_2$ (*Godchot,* C. r. **188**, 794). The dimethyl derivative is the product of an interesting pinacolin rearrangement of isopropyl-cyclohexyl-pinacol (cf. ring transitions p. 13). Its constitution was established by oxidation to *α-keto-β,β-dimethyladipic acid* (*Tarbouriech,* C. r. **156**, 75).

2,2,3-Trimethyl-cycloheptanone-1, $C_{10}H_{18}O$, has been converted by means of formic ester into *3,3,4-trimethyl-Δ^1-cycloheptene-1-aldehyde,* $C_{11}H_{18}O$ (French Pat. 744,344):



Δ^2-Cycloheptenone-1, *α,β-suberenone, tropilene,* 
$\begin{array}{l} CH_2—CH{=}CH \\ | \qquad\qquad\qquad > CO \\ CH_2—CH_2—CH_2 \end{array}$
, b.p. 186–188°, is formed by exhaustive methylation of tropine or tropidine methiodide (vol. IV), and by elimination of H-halide with aniline from α-bromo- or α-chloro-suberone. It gives suberone on catalytic reduction and adipic acid on oxidation (*Kötz*, Ber. **44**, 464; Ann. **400**, 72).

Δ^2-2-Methylcycloheptenone, 
$\begin{array}{l} CH_2—CH_2—CO \\ | \qquad\qquad\qquad > CMe \\ CH_2—CH_2—CH \end{array}$
, b.p. 200–205°. *Wallach* obtained the oxime of this compound by removing HCl from the nitrosochloride of Δ^1-Me-suberene (Ann. **345**, 145).

Cycloheptylidene-acetone, $C_7H_{12}{:}CHCOCH_3$, b.p. 98°/10 mm., and **Δ^1-Cycloheptenyl-acetone,** $C_7H_{11}CH_2COCH_3$, b.p. 95°/13 mm., are prepared from the corresponding substituted acetyl chlorides with MeZnI. *Semicarbazones,* m.p. 172–173° and 128–129° decomp. (*Kon* et al., J. **1929,** 1435).

2,6,6-Trimethyl-$\Delta^{2,4}$-cycloheptadienone-1, *eucarvone,* $C_{10}H_{14}O$, b.p. 86°/12 mm. (p. 249), is obtained by ring enlargement from the hydrobromide of the hydroaromatic compound carvone on removal of HBr. When exposed to air in alkaline alcoholic solution or when gently oxidised by H_2O_2 in MeOH it is converted, first into the substituted *cycloheptenone oxide,* $C_{10}H_{14}O_2$, b.p. 105–110°/20 mm., and then into the *mono-methyl-ether* of the corresponding *glycol,* $C_{11}H_{18}O_3$, b.p. 135–137°/20 mm. On autoxidation or by vigorous action of warm hydrogen peroxide water is split off with the formation of a bicyclic condensation product, $C_{20}H_{28}O_3$ (p. 153), of which two isomeric forms, m.ps. 215° and 217°, are known. Their *semicarbazones* melt at 266° and 254° resp. (*Treibs,* Ber. **66**, 1483).

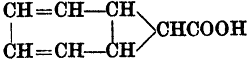
Carboxylic Acids. — **Cycloheptane-carboxylic acid,** *suberane carboxylic acid,* $C_7H_{13}CO_2H$, b.p. 139°/15 mm., *amide* m.p. 195°, has been prepared synthetically from **suberane-1,1-dicarboxylic acid,** the ester of which is formed in small quantity when 1,6-dibromohexane reacts with Na and malonic ester (*Haworth, Perkin,* J. **65**, 591). Other ways of obtaining suberane carboxylic acid are by treating suberyl bromide with Mg and CO_2 in Et_2O and by reducing various cycloheptene, cycloheptadiene and cycloheptatriene carboxylic acids. It gives with bromine and phosphorus **α-Bromo-suberane-carboxylic acid,** m.p. 93°.

This gives by loss of HBr **Δ^1-Cycloheptene-carboxylic acid,** *suberene carboxylic* acid, $C_7H_{11}COOH$, m.p. 54°, *amide* m.p. 134–135°, which is also formed when the isomeric **Δ^2-cycloheptenyl-carboxylic acid,** m.p. 19°, *amide* m.p. 158°, is heated with aqueous alkalis. *Willstatter* has obtained both these and other isomeric acids by reducing cycloheptatriene-carboxylic acids or their dihydrobromides (Ann. **317**, 234).

Cycloheptane-1,2,4-tricarboxylic acid, trans, m.p. 198–200°. The *triethyl ester,* b.p. 212–215°/30 mm., is a by-product in the preparation of the pentacarboxylic ester (see below) and gives the acid on hydrolysis with conc. HCl. The ethyl ester of cycloheptane-1,1,2,4,4-pentacarboxylic acid is obtained from pentane-α,α,ε,ε-tetracarboxylic ester and α,β-dibromo-propionic ester with Na (*Goldsworthy, Perkin,* J. **105**, 2665). **Cycloheptane-hexacarboxylic acid,** m.p. 177°, is converted by heat into the **1,3,5,6-tetracarboxylic acid,** m.p. 283° (*Meerwein,* J. pr. **104**, 199).

Cycloheptadiene-carboxylic acid, C_7H_9COOH, m.p. 78°, known as *hydrotropilidene carboxylic acid,* is a degradation product of hydro-ecgonidine, (vol. IV).

Cycloheptatriene-carboxylic acids, *tropilidene carboxylic acids,* C_7H_7COOH (see p. 166), α, m.p. 71°, *amide* m.p. 129°; β, m.p. 56°, *amide* m.p. 98°; γ, liquid, *amide* m.p. 90°; δ, m.p. 32°, *amide* 125°. The isomerism is due to a different arrangement of the three double bonds. The acids unite with HBr to form mono- and di-hydrobromides, and finally tri-hydrobromides, while energetic treatment with HBr results in rearrangement and in the formation of p-toluic acid. *Willstätter* has obtained these acids by decomposing the alkaloid ecgonine, which contains a 7-membered carbon ring like the related tropine (vol. IV) (Ber. **31**, 2498). *Braren* and *Buchner* (Ber. **33**, 684) have prepared them by rearrangement of *norcaradiene-carboxylic acid* (pseudo-phenylacetic acid). This compound is formed from benzene and diazo-acetic ester (I, 458), which react with liberation of nitrogen. Its formula is



$$\begin{matrix} CH{=}CH{-}CH \\ | \qquad\qquad | \\ CH{=}CH{-}CH \end{matrix}\!\!>\!CHCOOH$$

and it contains a six-membered ring condensed with a cyclopropane ring, cf. polynuclear alicyclic compounds, p. 165. *Carone*, a terpene ketone, contains a similar grouping (p. 248).

Cycloheptylidene-acetic acid, m.p. 54°, *anilide* m.p. 90–91° and **Δ^1-Cycloheptenyl-acetic acid,** b.p. 153°/17 mm., *anilide* m.p. 79–80°, are both formed when suberone is treated with bromo-acetic ester and Zn or Mg. The product of the reaction is an equilibrium mixture composed of 25–26°/₀ of the first and 74–75°/₀ of the second acid. On bromination the first acid gives *α,β-dibromo-cycloheptyl acetic acid,* and the second the isomeric *β,γ-acid,* m.ps. 125° and 102–103° resp. (*Kon* et al., J. **1929**, 1435).

1-Hydroxycycloheptane-carboxylic acid,

$$C_6H_{12} > C(OH)CO_2H + {}^1/_2\,H_2O,$$

melts in the anhydrous state at 79°. It has been prepared by *Willstätter* (Ber. **31**, 2505) from suberone with hydrogen cyanide, also from 1-bromosuberane carboxylic acid with aqueous baryta. PbO_2 oxidises it smoothly to suberone. Conc. hydrochloric acid or PCl_5 convert it into the *chloro-carboxylic acid,* m.p. 43° (*Spiegel*, Ann. **211**, 117; *Buchner*, Ber. **31**, 2004). **1-Aminocycloheptane carboxylic acid,** $C_7H_{12}\,(NH_2)COOH + H_2O$, m.p. of the anhydrous compound 306–307° (*Zelinsky*, Ber. **39**, 1730).

1-Hydroxycycloheptane-acetic acid, *cycloheptanol-acetic acid*

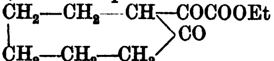
$$C_6H_{12} > C(OH)CH_2COOH.$$

The esters of this acid (*Me ester* b.p. 141–145°/12 mm., *Et ester* b.p. 134°/11 mm.) are the products of the reaction of suberone and bromo-acetic esters with Zn or Mg. When heated with $KHSO_4$ the esters lose water and are converted into unsaturated esters (cf. above). Hydroxycycloheptane-acetic acid reacts with hydrogen halides to form *bromo-* and *iodo-cycloheptane-acetic acids,* m.ps. 69° and 81°. These can be reduced to **cycloheptane-acetic acid,** $(C_7H_{13})\cdot CH_2COOH$, b.p. 165°/19 mm., *amide* m.p. 148° (*Wallach*, Ann. **353**, 301).

Cycloheptylidene-cyano-acetic ester, b.p. 160°/12 mm., has been prepared from suberone with cyano-acetic ester and piperidine. When reduced, it yields *cycloheptyl-cyanoacetic ester,* b.p. 149°/11 mm., which can be hydrolysed to *cycloheptyl-malonic acid,* m.p. 164·5° decomp. (*Vogel*, J. **1928**, 2013).

Cycloheptane-1-carboxylic-1-acetic acid, m.p. 159°, is formed from cycloheptylidene-cyanoacetic ester + KCN followed by hydrolysis by HCl. *Anhydride* m.p. 16° (*Vogel*, ib.). **Cycloheptane-1,1-diacetic acid,** m.p. 156–157°, has been synthesised by *Day*, *Kon* and *Stevenson* from suberone by condensing it with cyanoacetic ester by means of NH_3 and hydrolysing the dicyano-imide (J. **117**, 639). *Anhydride* m.p. 75–76°, *imide* m.p. 177–178°.

Ethyl cycloheptanone-2-oxalate,

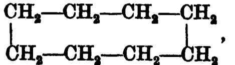


$$\begin{matrix} CH_2{-}CH_2{-}CH{-}COCOOEt \\ | \qquad\qquad\qquad\quad \\ CH_2{-}CH_2{-}CH_2 \end{matrix}\!\!>\!CO$$

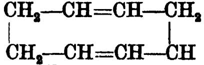
, b.p. 146–148°/13 mm., from suberone, oxalic ester and NaOEt, together with cycloheptanone-2-carboxylic ester, b.p. 135–138°/22 mm. (*Kötz*, J. pr. 88, 261; *Manske*, *Leitch*, Canad. J. Res **14**, B, 1).

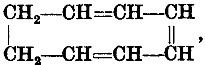
5. CYCLO-OCTANE GROUP

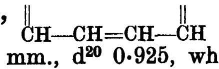
The doubly unsaturated hydrocarbons of the cyclo-octane group were, at one time, the object of special interest, because they were thought to be closely related to rubber, but the hypothesis that an eight-membered ring occurs in the caoutchouc molecule has proved to be erroneous. An alkaloid occurring in pomegranate bark, *pseudopelletierine*, which is closely related to tropine and tropinone, does, however, contain this ring and has served as a starting material for the synthesis of most of the compounds described below.

Cyclo-octane,  $\begin{array}{l} CH_2—CH_2—CH_2—CH_2 \\ \mid \qquad\qquad\qquad\quad \mid \\ CH_2—CH_2—CH_2—CH_2 \end{array}$, m.p. 13–14°, b.p. 148·5–149·5°, d_4 0·830, is obtained when either cyclo-octene or β-cyclo-octadiene is reduced on Pt or Ni with H_2, and also from the hydrazone of cyclo-octanone with KOH (*Vogel*, J. **1929**, 721; *Zelinsky*, Ber. **63**, 148). It is oxidised by nitric acid to suberic acid (*Willstätter*, Ber. **41**, 1484).

Cyclo-octene, C_8H_{14}, b.p. 143–144°, is obtained, together with polymerised products, when cyclo-octanol is treated with phthalic anhydride or with naphthalene-sulphonic acid (*Godchot*, C. r. **185**, 1202; *Ruzicka*, Helv. **14**, 319) and also by ring enlargement on heating cycloheptyl-carbinol (p. 71) with ThO_2 (*Rosanov*, C. 1930 II 229). It unites with phenyl azide (*Alder*, Ann. **501**, 8). **1-Methyl-Δ^1-cyclo-octene,** b.p. 158–160°, is obtained by distilling in vacuo the unstable tertiary alcohol obtained from cyclo-octanone and MeMgI. *Nitroso-chloride* m.p. 107–108° (*Godchot*, l. c.).

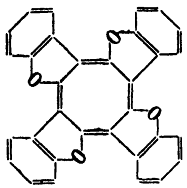
$\Delta^{1,5}$-Cyclo-octadiene,  $\begin{array}{l} CH_2—CH{=}CH—CH_2 \\ \mid \qquad\qquad\qquad\quad \mid \\ CH_2—CH{=}CH—CH \end{array}$, b.p. 39°/16 mm., d_4 0·884, is formed, together with small amounts of an isomeric bicyclic hydrocarbon (p. 167), by distillation of the quarternary ammonium base obtained by exhaustive methylation of N-methyl-granatenine, a reduction product of ψ-pelletierine (vol. IV) (See the similar synthesis of cycloheptadiene from tropane p. 70.) Cyclo-octadiene is a mobile oil of penetrating odour; the vapour is poisonous. It polymerises readily, even at ordinary temperature, and with explosive rapidity when heated, forming a *dicyclo-octadiene*, $(C_8H_{12})_2$, m.p. 114°, and a *polycyclo-octadiene*, $(C_8H_{12})_x$, an amorphous mass melting above 300°. Cyclo-octadiene is converted by ozone into the *diozonide*, $C_8H_{12}O_6$, which is decomposed by water, forming succinic dialdehyde. It combines with HBr to give a *dihydrobromide*, $C_8H_{14}Br_2$, b.p. 150°/12 mm., which yields, by the action of caustic potash or of quinoline, a **β-cyclo-octadiene,** b.p. 143°, isomeric with the starting material. This compound has a pleasant odour and does not show any tendency to polymerise (*Willstatter*, Ber. **40**, 957).

Cyclo-octatriene,  $\begin{array}{l} CH_2—CH{=}CH—CH \\ \mid \qquad\qquad\qquad\quad \| \\ CH_2—CH{=}CH—CH \end{array}$, b.p. 147·2–148·2°, has been synthesised by *Willstatter* (Ber. **44**, 3423; **46**, 523) by distilling the methylated base obtained from α-dimethyl-granatenine (vol. IV) in a vacuum. It is a mobile oil with a sweetish odour, and gives an oily dibromide.

Cyclo-octatetrene,  $\begin{array}{l} CH—CH{=}CH—CH \\ \| \qquad\qquad\qquad\quad \| \\ CH—CH{=}CH—CH \end{array}$ is a yellow oil, m.p. —27°, b.p. 42·2–42·4°/17 mm., d^{20} 0·925, which has been obtained, also by *Willstätter*, from the methiodide of tetramethyldiamino-cyclo-octadiene by means of Ag_2O. *Dibromide*, m.p. 70–71·5° (Ber. **44**, 3442; **46**, 517). Though its formula seems somewhat similar to the *Kekule* formula for benzene, cyclo-octatetrene is very unlike benzene and displays a strongly unsaturated and distinctly aliphatic character. It resinifies on standing in air or when treated with a mixture of nitric and sulphuric acids, it is oxidised violently by $KMnO_4$ and is readily reduced catalytically to the saturated cyclo-octane.

The reasons for this profound difference between cyclo-octatetrene and benzene are not yet fully understood, and further work on the behaviour of the cyclo-octatetrene derivatives is needed. It may be connected with certain requirements in space arrangement which must be satisfied in order that a completely conjugated system, like benzene, may exist. The quantum-mechanical aspect of the problem has been discussed by *Penney* (Proc. Roy. Soc. A **146**, (1934), 223); he finds that in ring compounds of the general formula $(CH)_n$ the effect of the various exchange energies and interactions leads to a maximum of stability when $n = 6$.

When the acetate of 2-hydroxy-dicoumarone, $C_{16}H_{10}O_3$, which is a condensation product of 2-coumaranone (vol. III), is heated with HCl and acetic acid under pressure, a reddish product is formed which has the dimolecular formula, $C_{32}H_{16}O_4$, m.p. > 300°, with sublimation. It is a complicated derivative of cyclo-octatetrene (*Fries*, Ber. **44**, 114):

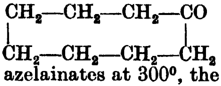


Cyclo-octanol, *azelaol,* $C_8H_{15}OH$, m.p. 14–15°, b.p. 106–108°/22 mm., *phenylurethane* m.p. 62°, is prepared from cyclo-octanone (see below) by reduction with Na and EtOH. The *pinacol,* $C_8H_{14}(OH)\cdot(HO)C_8H_{14}$, m.p. 93–94°, is formed at the same time (*Godchot,* C. r. **185**, 1202; *Ruzicka,* Helv. **14**, 1319). It is also obtained from cycloheptylmethyl-amine (p. 71) by ring enlargement by means of nitrous acid (*Rabe,* Ber. **31**, 1987; *Aschan,* Ber. **32**, 1761; *Wallach,* Ann. **353**, 318). **α-Methylcyclo-octanol** is known in two forms b.ps. 100° and 103°/16 mm., one of which is obtained by reducing the corresponding ketone catalytically, and the other by reducing it chemically. **α,α-Dimethyl-cyclo-octanol,** b.p. 91–92°/6 mm., is obtained from the ketone with Na and absolute EtOH (*Godchot,* Chimie et Ind. **1933**, Special No. 6 bis).

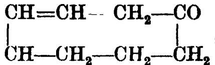
Cyclo-octylcarbinol, $C_8H_{15}CH_2OH$, b.p. 114–116°/12 mm., is obtained by means of N_2O_3 from **Cyclo-octyl-methylamine,** b.p. 92–94°/12 mm., which is prepared by dehydrating cyclo-octanone cyanohydrin and reducing the cyclo-octenylcyanide thus formed. **β-Cyclo-octyl-ethyl alcohol,** b.p. 125–127°/12 mm., is the reduction product of the ester of cyclo-octane acetic acid (see below) (*Ruzicka,* Helv. **9**, 399; **14**, 319).

Cyclo-octene oxide, m.p. 45°, is obtained from cyclo-octene with perbenzoic acid (*Godchot,* C. r. **192**, 962).

Cyclo-octane aldehyde, $C_8H_{15}CHO$, b.p. 76–78°/16 mm., has been prepared by *Ruzicka* by the action of alcoholic KOH on the glycidic ester, b.p. 125°/25 mm., obtained from cyclo-octanone with Na and chloroacetic ester (Helv. **14**, 1319).

Cyclo-octanone, *azelaone,*  $\begin{array}{l} CH_2—CH_2—CH_2—CO \\ | \qquad\qquad\qquad\qquad\quad | \\ CH_2—CH_2—CH_2—CH_2 \end{array}$, is obtained as a distillation product of Ca and Th azelainates at 300°, the latter salt giving a yield of 25% (*Ruzicka,* Helv. **9**, 339). The reaction is similar to the conversion of suberates into suberone. *Vogel* has prepared this ketone from the free acid by applying his Fe-BaO method (J. **1929**, 721), while the best way is to treat azelaic dinitrile with phenyl-ethyl-lithium-amide (cf. p. 21 method 8 and p. 79, large rings). Azelaone is an oil very similar to suberone in odour; m.p. 42°, b.p. 197–198°, *oxime* m.p. 35–36°, *semicarbazone* m.p. 168–169°. *Cyclohexadecane-*1,9-*dione,* m.p. 83–84°, is a by-product in the synthesis. Azelaone is converted into suberic acid when oxidised with $KMnO_4$ and into azelaol when reduced with Na and EtOH.

Godchot and *Cauquil* have obtained alkylated cyclo-octanones by a similar method from α- and β-alkylated azelaic acids (C. r. **192**, 962; Germ. Pat. 580,713).

Δ³-Cyclo-octenone-1, *granatal,* 

$$\begin{array}{l} CH{=}CH{-}CH_2{-}CO \\ |\qquad\qquad\qquad\quad | \\ CH{-}CH_2{-}CH_2{-}CH_2 \end{array}$$

, b.p. 73–74°/8 mm. is obtained from β-dimethyl-granatenine (vol. IV) with HCl (*Willstätter*, Ber. **44**, 3334).

Acetyl-cyclo-octane, *semicarbazone* m.p. 181°, is prepared from cyclo-octene with acetyl chloride and $SnCl_4$ and subsequent hydrogenation (*Ruzicka*, Helv. **14**, 1319).

Cyclo-octadione-1,5, m.p. 20–24°, b.p. 107–110°/14 mm., *disemicarbazone* m.p. 186°, has been isolated by *Harries* (Ber. **46**, 733, 2590) from the products of ozonisation of regenerated para-caoutchouc, a fact which at one time was held to support an 8-ring formula for natural caoutchouc.

Cyclo-octane-carboxylic acid, b.p. 150°/19 mm., is prepared by oxidising the carbinol with CrO_3 (*Ruzicka*, Helv. **9**, 389), or from cyclo-octyl-Mg-Br with CO_2 (*Godchot, Cauquil*, Chimie et Ind. **1933**, Special No. 6 bis). *Amide*, m.p. 191°. **Cyclo-octane-acetic acid,** b.p. 130°/1 mm., is prepared by catalytic reduction of **Cyclo-octenyl-acetic acid,** b.p. 135–137°/1–2 mm., which is obtained through the hydroxy-acid from cyclo-octanone with Zn and bromoacetic ester (*Ruzicka*, Helv. **14**, 1319).

6. COMPOUNDS WITH NINE TO THIRTY-FOUR CARBON ATOMS IN THE RING

This group of related compounds has only recently been studied in any detail. Though some of its members have been known for many years, either their ring structure was not recognised, or they had not been obtained in a pure state. The interest attaching to the group is considerable both from the theoretical and the industrial point of view.

The existence of these compounds conflicts with *Baeyer's* strain theory, which, on the assumption that the ring is uniplanar, predicts a strain increasing with the number of members in the ring. The existence of such a strain is not, however, suggested by the striking stability of the saturated members of the group, and, especially in view of observations made in the smaller rings, the conclusion has been drawn that the rings are non-planar. The values of the heats of combustion, which throw light on the energy content and hence the ring strain in a system, give support to this conclusion (see p. 10).

The view that the space arrangement of the multi-membered rings is a kind of closed zig-zag doubled chain very similar to that found in the aliphatic hydrocarbons, finds support in other of their physical properties, such as melting point, density, molecular volume, compressibility etc. These have been discussed already in the introduction of the section on alicyclic carbon rings (p. 8).

X-ray investigation of certain of the cyclic ketones in the liquid state also shows that the molecule is longer in one direction than the other (*Katz*, Z. Phys. **46**, 392). The ketones from C_{15} to C_{30} have been studied as monomolecular films on water (*Buchner*, *Katz*, *Samwel*, Z. phys. Chem. B **5**, 327) and compared with the long chain fatty acids; it is known that films of the latter consist of hydrocarbon chains standing vertically to the water surface. The higher ketones closely resemble the fatty acids and their molecules must consist essentially of a doubled chain; with the lower members there are abnormalities, the causes of which are not yet fully known.

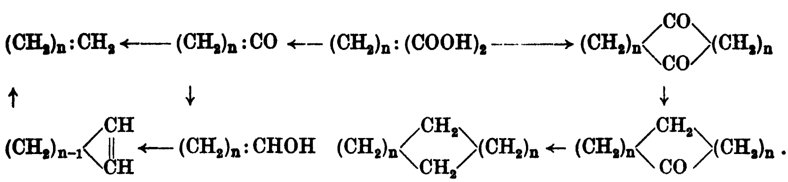
Some ketones of this series, both saturated and unsaturated, are industrially important since they represent, either as such or in the form of their lactones, the odoriferous principles of musk, a most valuable ingredient in perfumery.

The first investigation into this subject was carried out in 1906 by *H. Walbaum* (J. pr. **73**, 488). Musk is contained in a gland of the male musk deer (*Moschus moschiferus, Cervidae*), of Eastern and Central Asia. The odoriferous principle can be distilled with steam. After removing the impurities, *Walbaum* succeeded in isolating a ketone, which he called *muscone* and to which, with great probability, he could attribute the formula $C_{16}H_{30}O$. He prepared a number of characteristic derivatives. This is the odoriferous principle of the valuable musk perfume. The odoriferous principle of civet, the secretion of a gland common to both sexes of the Abyssinian civet cat *Viverra civetta,* was isolated by *Sack* in 1914 (Chem.-Ztg. **39**, 538). After removing acid and basic impurities he obtained a ketone $C_{17}H_{30}O$, *civetone*, and characterised it by a number of derivatives. *L. Ruzicka* entered this field of research in 1926. With the help of numerous co-workers he developed methods suitable for the systematic synthesis of compounds of this class and for disclosing their inter-relationships; these are described in a long series of valuable papers published in the Helvetica Chimica Acta, vols. **9** to **14**. We owe most of our present knowledge of the subject to his work. Immediately after the publication of *Ruzicka's* first paper on the structure of civetone, *Walbaum* published (J. pr. **113**, 155, 166) the observations which he had made years before on the transformation products of muscone.

The chief starting materials for the synthesis of these polycarbocyclic compounds are the saturated and unsaturated ω,ω'-dicarboxylic acids of the straight-chain aliphatic hydrocarbons. New methods of preparation for these acids were discovered by *Chuit*. Their Th- and Y-salts are distilled in a high vacuum at 300°, metal turnings being added to aid in heat conduction. Ring ketones containing one C less than the acids are formed in a relatively good yield, as in the preparation of cyclic ketones of lower molecular weight. There are two by-products of the reaction: the first is the methyl alkyl ketone, which is formed by a secondary reaction of the dicarboxylic acid, and can be readily removed with bisulphite; the second is the symmetrical monocyclic diketone of twice the molecular weight, which can be separated owing to its higher boiling point. The latter side-reaction makes it possible to obtain carbon rings containing up to thirty-four carbon atoms.

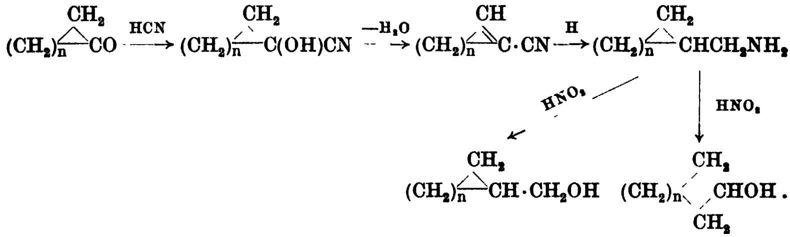
The monoketones are reduced by Na + EtOH or AmOH to alcohols; these are dehydrated by $KHSO_4$, naphthalene-sulphonic acid etc. to unsaturated cyclic hydrocarbons and these, finally, are hydrogenated to saturated cycloparaffins. The reduction can be modified to furnish di-tertiary glycols (pinacols) composed of two cyclo-alkyl residues, and other derivatives. When treated with *Caro's* acid the ketones take up oxygen in the position adjacent to the CO-group and the lactones mentioned above are formed. Some of these, or their parent ω-hydroxy-fatty acids have been found in constituents of certain plants (*Kerschbaum,* Ber. **60**, 902). The monoketones are transformed into hydrocarbons by the *Clemmensen* reduction method, or by treating their semicarbazones with NaOEt in a sealed tube at 180°, while the diketones, when subjected to *Clemmensen's* reaction, give a mixture of the corresponding monoketone and hydrocarbon.

The following general scheme of reactions is given instead of data for each individual compound;



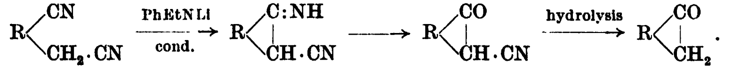
As an example, the cyclic monoketone $C_{20}H_{38}O$ has been prepared either by distilling the Th-salt of the dicarboxylic acid $C_{19}H_{38}(COOH)_2$, or by the partial reduction of the diketone $C_{20}H_{36}O_2$, which is obtained as a by-product, together with the ketone $C_{10}H_{18}O$, on distilling the Th-salt of the dicarboxylic acid $C_9H_{18}(COOH)_2$.

Another route to multi-membered rings has been discovered by *Demjanov* (C. 1903 I 818; 1904 I 1214; cf. *Ruzicka*, Helv. **9**, 399), in which a cyclic ketone is converted into a secondary alcohol with one more carbon atom in the ring, according to the following scheme:



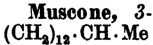
In the last reaction of the series two products can be formed, one the normal product with the same number of atoms in the ring, and an abnormal product which is the result of ring enlargement. The side-reaction does not take place with the lower cyclic ketones up to cyclohexanone; with cyclo-octanone, however, the reaction product contains $60^0/_0$ of the cyclo-octyl carbinol which would be expected, and $40^0/_0$ of cyclononanol. Another side-reaction which occurs is the loss of water from the secondary alcohol to give a hydrocarbon with a double bond in the ring.

The yield of ketones obtained by distilling the rare earth salts of dicarboxylic salts falls with increasing molecular weight to a few percent and even less. Much better yields are obtained by a method devised by *K. Ziegler*, which consists of the ring closure of dinitriles by means of phenyl-ethyl-lithium-amide as a condensing agent. He prepared suberone with a yield of $80-90^0/_0$, cyclo-octanone with a yield of $30^0/_0$, the ketones derived from cyclopentadecane and cycloheptadecane in yields as big as $37-44^0/_0$ and $52^0/_0$. These yields are approximately ten times greater than those previously obtained. The reaction proceeds according to the general scheme (Ann. **504**, 94; Ber. **67** A, 139):



In accordance with the historical development of the subject an account is first given of the compounds of this group which occur in nature and of their derivatives, and then of the compounds obtained synthetically, arranged according to their functional groups, together with their most important constants.

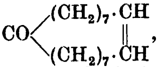
Muscone, *3-(β-)methyl-cyclopentadecanone-1, 3-methyl-exaltone,* $C_{16}H_{30}O$,



$\begin{array}{l}(CH_2)_{12}\cdot CH\cdot Me\\ |\qquad\qquad\; |\\ CO——CH_2\end{array}$

, b.p. 142–143°/2 mm., $[\alpha]_D$ — 10°6′ forms about 1·2% of the contents of the musk gland. It is a clear, somewhat oily liquid and has a very strong characteristic odour. *Oxime* m.p. 45°, *iso-oxime* m.p. 90–95°, *semicarbazone* m.p. 134°. It is very stable under ordinary circumstances towards $KMnO_4$, acids and alkalis. Reduction with Na and amyl alcohol gives the corresponding alcohol, **muscol,** $C_{16}H_{31}OH$, m.p. 38°, b.p. 140°/1 mm., $[\alpha]_D$ + 14·9°, *phenylurethane* m.p. 97–98°. This gives the unsaturated hydrocarbon **muscene,** $C_{16}H_{30}$, b.p. 120°/1 mm., $[\alpha]_D$ — 8·8°, by loss of water. The ketone is converted by the *Clemmensen* reduction process into the saturated hydrocarbon **muscane,** m.p. — 19°, and by CrO_3-oxidation into methyl-tridecane-dicarboxylic-1,13-acid, m.p. 68°, together with simpler dicarboxylic acids. Syntheses of muscone have been carried out by *Ziegler* (Ann. **512,** 164) and by *Ruzicka* and *Stoll* (Helv. **17,** 1308).

Civetone, *Δ^9-cycloheptadecene-1-one,* $C_{17}H_{30}O$,



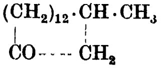
$CO\begin{array}{l}\diagup(CH_2)_7\cdot CH\\ \qquad\qquad\quad\|\\ \diagdown(CH_2)_7\cdot CH\end{array}$

, m.p. 31°, b.p. 145°/0·5 mm., and the corresponding alcohol, $C_{17}H_{31}OH$, **civetol,** m.p. 65°, occur together in civet in approximately equal amounts of $2^1/_2\%$–$3^1/_2\%$ of each. The alcohol is converted into the ketone by oxidising with CrO_3 or by catalytic dehydrogenation. The ketone is also obtained from the Th-salt of Δ^7-hexadecene-1,16-dicarboxylic acid. *Oxime* m.p. 92°, *semicarbazone* m.p. 187°. When hydrogenated under mild conditions by *Paal's* method civetone is converted into the saturated compound **dihydro-civetone,** *cycloheptadecanone,* $C_{17}H_{32}O$, m.p. 63°, which is isomeric with civetol; is also obtained by the general method of synthesis from cyclohexadecane-1,16-dicarboxylic acid. *Iso-oxime* m.p. 123–124°, *semicarbazone* m.p. 191°. Both the saturated and the unsaturated ketone have a strong odour of musk. When hydrogenated more vigorously civetone gives **dihydrocivetol,** $C_{17}H_{33}OH$, m.p. 80°, and this by loss of water gives the unsaturated hydrocarbon **civetane,** $C_{17}H_{32}$, m.p. 47°, which is also obtained from civetone by *Clemmensen's* method or through the semicarbazone. As a by-product of hydrogenation **dihydrocivetane,** *cycloheptadecane,* $C_{17}H_{34}$, m.p. 65°, is formed. When civetone is oxidised with $KMnO_4$, 8-ketopentadecane-1,15-dicarboxylic acid, $CO[(CH_2)_7COOH]_2$, m.p. 115–116°, azelaic acid $C_9H_{16}O_4$, m.p. 105°, and suberic acid $C_8H_{14}O_4$, m.p. 140°, are formed. On treatment with CrO_3 dihydrocivetone gives pentadecane-1,15-dicarboxylic acid, m.p. 110–112°, which is also formed by the action of ozone on civetane. Civetane and $KMnO_4$ give tetradecane-1,14-dicarboxylic acid, m.p. 116°.

Syntheses of *unsaturated cyclic ketones* of the civetone type have been carried out by *Ruzicka* (Helv. **15,** 1459) from unsaturated dicarboxylic acids.

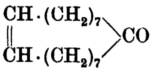
There is a remarkable relationship between muscone and civetone on one hand and palmitic and oleic acids on the other as was pointed out by *Ruzicka*:

Muscone



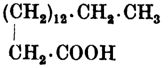
$\begin{array}{l}(CH_2)_{12}\cdot CH\cdot CH_3\\ |\qquad\qquad\; |\\ CO\text{----}CH_2\end{array}$

Civetone



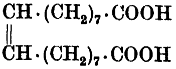
$\begin{array}{l}CH\cdot(CH_2)_7\diagdown\\ \|\qquad\qquad\quad CO\\ CH\cdot(CH_2)_7\diagup\end{array}$

Palmitic acid



$\begin{array}{l}(CH_2)_{12}\cdot CH_2\cdot CH_3\\ |\\ CH_2\cdot COOH\end{array}$

Oleic acid



$\begin{array}{l}CH\cdot(CH_2)_7\cdot COOH\\ \|\\ CH\cdot(CH_2)_7\cdot COOH\end{array}$.

Hydrocarbons: Cyclononane, b.p. 170–172°. **Cyclodecane,** m.p. 9·6°, b.p. 201°. **Cyclododecane,** m.p. 60–61°, b.p. 118°/18 mm. **Cyclotridecane,** m.p. 17–18°, m.p. 112–113°/9 mm. **Cyclotetradecane,** m.p. 52–53°, b.p. 143°/16 mm. **Cyclopentadecane,** "*exaltane*", m.p. 60–61°, b.p. 110–115°/1 mm., b.p. 147–148°/12 mm. **1-Methyl-Δ^1-cyclopentadecene,** b.p. 152–153°/12 mm. **Cyclohexadecane,** m.p. 56–57°, b.p. 170–171°/20 mm. **Cycloeicosane,**

m.p. 45–46°. **Cyclodocosane,** m.p. 45–46°. **Cyclotricosane,** m.p. 50°. **Cyclotetracosane,** m.p. 46–47°. **Cyclohexacosane,** m.p. 41–42°, b.p. 218–219°/0·5 mm. **Cyclo-octacosane,** m.p. 47–48°, b.p. 213–214°/0·25 mm. **Cyclononacosane,** m.p. 46–47°, b.p. 215°/1·1 mm. **Cyclotriacontane,** $C_{30}H_{60}$, m.p. 53–54°. **Cyclopentadecine,** $C_{15}H_{26}$, b.p. 158–159°/14 mm. and **Cycloheptadecine,** $C_{17}H_{30}$, b.p. 127–128°/0·25 mm., from the corresponding cyclo-olefin-dibromides with alcoholic KOH (*Ruzicka* et al., Helv. **16**, 498).

Alcohols: **Cyclononanol,** b.p. 100–102°/12 mm., from cyclo-octylmethylamine with HNO_2 (*Zelinsky*, Ber. **40**, 3277, *Willstätter* et. al., ib. 3876; *Ruzicka* et al., Helv. **9**, 399). **Cyclopentadecanol,** *exaltol,* m.p. 80–81°, b.p. 145°/0·3 mm. **1-Methylcyclopentadecane-1-ol,** *methylexaltol,* from the ketone with MeMgI, m.p. 85–86°.

Ketones: **Cyclononanone,** m.p. 29°, b.p. 93–95°/12 mm. (*semicarbazone* m.p. 184–185°). **Cyclodecanone,** m.p. 16–17°, b.p. 106–107°/13 mm. (*semicarbazone* m.p. 205–207°). **Cyclo-undecanone,** m.p. 9–10°, b.p. 108°/12 mm. (*semicarbazone* m.p. 203–204°). **Cyclododecanone,** m.p. 60–61°, b.p. 125°/12 mm. (*semicarbazone* 226–227°). **Cyclotridecanone,** m.p. 30–32°, b.p. 138°/12 mm. (*semicarbazone* m.p. 207–208°). **Cyclotetradecanone,** m.p. 52–53°, b.p. 155°/12 mm. (*semicarbazone* 197–198°). **Cyclopentadecanone,** *exaltone, apomuscone,* m.p. 63°, b.p. 120°/10 3 mm. (*semicarbazone* m.p. 187–188°). **2-(α)-Methylcyclopentadecan-1-one,** b.p. 171–173°/12 mm. from exaltone by methylating with MeMgI (*semicarbazone* m.p. 149–150°). **4-(γ)-Methylcyclopentadecanone,** m p. 28–29°, b.p. 125°/0·5 mm. (*semicarbazone* m.p. 161–162°). **5-(δ-)Methylcyclopentadecanone,** b.p. 125°/0·5 mm. (*semicarbazone* m.p. 164–165°). **Cyclohexadecanone,** m.p. 63–64°, b.p. 138°/0·3 mm. (*semicarbazone* m.p. 180°). **Cycloheptadecanone,** *dihydrocivetone* b.p. 145°/1 mm. **Cyclo-octadecanone,** m.p. 72°, b.p. 158°/0·3 mm. (*semicarbazone* m.p. 184°). **Cyclononadecanone,** m.p. 72°, b.p. 160°/0·3 mm. **Cyclo-eicosanone,** m.p. 58–59°, b.p. 170–171°/0·3 mm. (*semicarbazone* m.p. 179–180°). **Cycloheneicosanone,** m.p. 45–46°, b.p. 176–177°/0·3 mm. **Cyclodocosanone,** m.p. 30–32°. **Cyclotricosanone,** m.p. 39°. **Cyclotetracosanone,** m.p. 35–36°, b.p. 233–238°/0·4 mm. **Cyclohexacosanone,** m.p. 41–42°, b.p. 208–212°/0·3 mm. **Cyclo-octacosanone,** m.p. 44–45°, b.p. 210°/0·25 mm. **Cyclononacosanone,** m.p. 45–47°, b.p. 220°/0·1 mm. **Cyclotriacontanone,** m.p. 53–54° (*Ruzicka* et al., Helv. **9**, 249; **11**, 686; **13**, 1152; **14**, 1319; **16**, 493; *Ziegler* and *Aurnhammer*, Ann. **513**, 43).

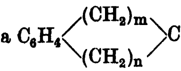
The odour of the ketones up to C_{12} resembles that of camphor, C_{13} is rather like cedar wood with a faint suggestion of musk, C_{14} smells distinctly of musk, and this odour reaches it full strength in C_{15} and its derivatives with Me in 3-, 4- and 5-positions The odour is weaker in the 2-methylated ketone and decreases progressively from C_{16} to C_{18}.

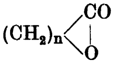
Ring substituted derivatives of this group are described by *Ruzicka*, Helv. **14**, 1319.

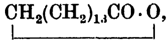
Diketones: **Cyclodecane-1,6-dione,** m.p. 100° (*dioxime* m.p. 231°), from $\Delta^{9,10}$-octalin with O_3 (*W. Huckel* et al., Ann. **474**, 121; Ber. **66**, 563). **Cyclohexadecane-1,9-dione** (abbrev.: C_{16}-1,9-dione), m.p. 83–84°. C_{18}-1,10-dione, m.p. 96–97°. C_{20}-11-dione, m.p. 51°. C_{22}-1,12-dione, m.p. 55–56°. C_{24}-1,13-dione, m.p. 64–65°. C_{26}-1,14-dione, m.p. 68–69°. C_{28}-1,15-dione, m.p. 72–73°. C_{30}-1,16-dione, m.p. 78–79°. C_{32}-1,17-dione, m.p. 77–78°. C_{34}-1,18-dione, m.p. 84° (*Ruzicka* et al., Helv. **11**, 496; **13**, 1152; **14**, 1319).

Triketones: $C_{33}H_{60}O_3$, m.p. 75–76°; $C_{45}H_{84}O_3$, m.p. 89°.

Unsaturated Ketones: **Cyclohexadecene-8-one-1,** m.p. 23°, from heptadecene-8-dicarboxylic acid-1,17; **cyclo-octadecene-9-one-1,** m.p. 38°, from nonadecene-9-dicarboxylic acid-1,19.

For *bicyclic ketones* of the general formula  $C_6H_4\left\langle\begin{matrix}(CH_2)_m\\(CH_2)_n\end{matrix}\right\rangle CO$ see *Ruzicka*, Helv. **15**, 1220.

Some of the cyclic ketones mentioned above give rise to large ring ω-lactones of the general form  $(CH_2)_n\left\langle\begin{matrix}CO\\|\\O\end{matrix}\right.$, when treated with *Caro's* acid. Several of these have a strong odour of musk. The following may be mentioned:

Lactone, $C_{15}H_{28}O$,  $\underbrace{CH_2(CH_2)_{13}CO\cdot O}$, *exaltolide,* m.p. 31–32°, b.p. 171–174°/14 mm. from exaltone. **Lactone,** $C_{17}H_{32}O_2$, m.p. 40–41°, b.p. 152–153°/2 mm. from dihydrocivetone. The **lactone,** $C_{16}H_{30}O_2$, *dihydro-ambrettolide,* m.p. 33–34°, b.p. 188°/15 mm., is also obtained from ambrettolide (1, 454) by hydrogenation (*Kerschbaum*, Ber. **60**, 902; *Ruzicka*, Helv. **11**, 1159; *Stoll*, Helv. **18**, 1087; *Carothers*, Am. **57**, 935; Brit. Pat. 294,602, 306,352).

Ib. MONONUCLEAR HEXACARBOCYCLIC OR HYDROAROMATIC COMPOUNDS

CYCLOHEXANE DERIVATIVES

BY FRANK ROCHUSSEN

It was pointed out in the introduction to the carbocyclic compounds that the hydroaromatic compounds would be separated from the series of homologous ring systems and treated in a separate chapter as a class of their own. While they are related to the benzene derivatives and can be converted into them, they are not aromatic in chemical character. Their behaviour and that of the homologous ring systems resembles that of aliphatic compounds. This fact is the reason for placing them here between the aliphatic and the mononuclear aromatic compounds. Together with the polynuclear aliphatic compounds which follow and with the terpene group they form a natural bridge between the two main groups of organic substances, the chain compounds and the benzene derivatives.

The parent hydrocarbon of the hydroaromatic compounds is cyclohexane (hexahydrobenzene), to which cyclohexene (tetrahydrobenzene) and cyclohexadiene (dihydrobenzene) are related, just as a paraffin is related to an olefin and a diolefin with the same number of carbon atoms.

In their chemical behaviour the cyclohexanes, which are isomeric with the olefins which contain the same number of carbon atoms, resemble the paraffins, and they are cycloparaffins (see p. 1). Tetrahydrobenzene is a cyclo-olefin and dihydrobenzene a cyclo-diolefin; benzene itself, on *Kekule*'s formula, is the simplest possible cyclotriolefin (see p. 2 and vol. III).

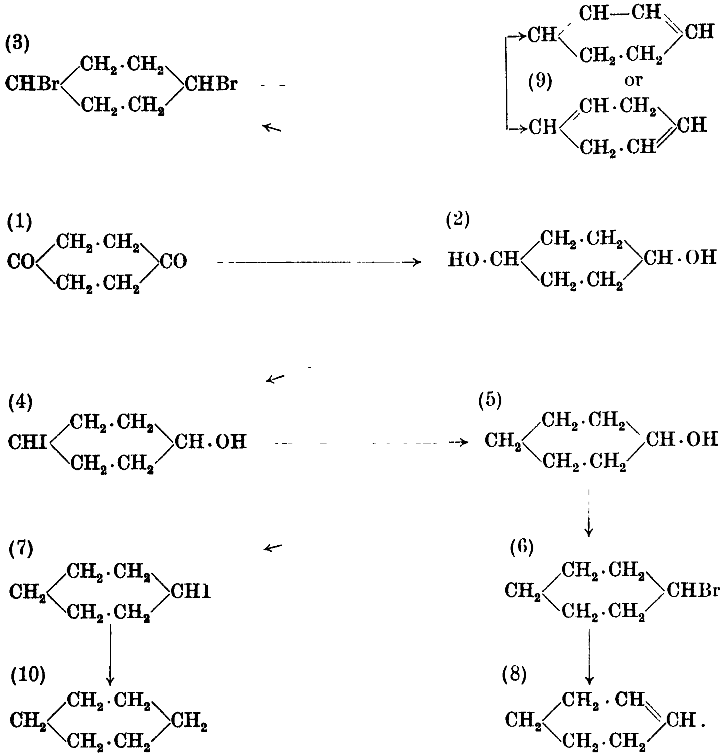
The reduction of aromatic compounds to cyclohexane derivatives does not, in general, take place at all easily. The first successful method was discovered in 1897 by *Sabatier* and *Senderens*, and consists in passing the vapour of the aromatic compound mixed with excess of hydrogen over hot finely-divided nickel; by this means aromatic hydrocarbons, phenols and anilines can be readily reduced to the corresponding cyclohexane compounds (Ann. chim. phys. (8) **4**, 319; **10**, 527).

This classical method of reduction has been developed in many directions by a number of investigators (*Paal, Willstätter, Adams, Adkins* and others) and by industrial organisations (*I.G. Farbenindustrie, Deutsche Hydrierwerke, Imperial Chemical Industries*, etc.). As catalysts for hydrogenation Pd-black, Pt-black, Pt-oxide, Fe, Cu etc. are used as well as Ni; sometimes the metal is deposited on the surface of an inert substance, such as the sulphate or carbonate of an alkaline earth. In many cases the catalytic reduction can also be carried out at a low temperature, e.g. in solvents such as EtOH and AcOH at room temperature.

When aromatic compounds are subjected to this process of catalytic hydrogenation, all the theoretically possible geometrical or optical isomers are formed as a rule. They can be separated by the ordinary methods. A rule put forward by *Skita* (Ann. **431**, 1) says that cis isomers of hydrocarbons, alcohols and amines are formed preferentially when the reduction is carried out in acid solution, while trans isomers are formed in alkaline or neutral solution. More recently, however, exceptions to this rule have been found both by *Skita* himself (Ber. **56**, 1014; **68**, 1346) and others (*Auwers*, J. pr. **124**, 209), and it must be applied with caution in questions of the configuration of geometrical isomers. The density and refractive index of a cis form are as a rule higher and the molecular refraction is lower than the corresponding values for a trans form (rule of *Auwers* and *Skita*, Ann. **420**, 91; Ber. **53**, 1792; see condensed ring systems p. 171). Trans isomers show very little tendency to undergo change of configuration, but the cis isomers are less stable. Rules which hold good for reduction with nascent hydrogen, e.g. the 1,4-addition to conjugated double bonds, cannot be applied in all cases to catalytic reduction. The mechanism of catalytic reduction has been investigated by *Polanyi* (Trans. Farad. Soc. **30** (1934), 1171). A survey of hydrogenations carried out with Pt or Pd in solvents has been published by *Vavon*, Bull. **41** (1927), 1253.

Berthelot (1867) first effected the reduction of benzene to cyclohexane. It was obtained pure by *Baeyer* (1894) in the course of an investigation in which he demonstrated how the simplest representatives of the hydroaromatic bodies — cyclohexane, cyclohexene and cyclohexadiene — could be prepared from cyclohexane-1,4-dione, a decomposition product of succinosuccinic ester (p. 112). Before beginning a detailed description of the hydroaromatic hydrocarbons, it may be well briefly to indicate the nature of *Baeyer's* experiments by means of a diagram. The numbers following the names refer to the formulae in the diagram.

Cyclohexane-1,4-dione (1) can be reduced to quinitol (2), which is converted by HBr into 1,4-dibromo-cyclohexane (3), and by HI mainly into the iodohydrin of quinitol (4), and partly into diiodo-cyclohexane. The iodohydrin can be reduced to cyclohexanol (5), which can be obtained more simply from cyclohexanone (p. 109); with HBr or HI, cyclohexanol gives bromocyclohexane (6) or the corresponding iodo compound (7). If bromo-cyclohexane is heated with quinoline cyclohexene (tetrahydrobenzene) (8) is formed, and similarly dibromo-cyclohexane gives cyclohexadiene (dihydrobenzene) (9). Iodo-cyclohexane (7) is reduced by zinc dust and acetic acid to cyclohexane (10):



The linkages in benzene are in a fundamentally different state, because of the complete conjugation of the double bonds, from those in its reduction products, cyclohexadiene, cyclohexene and cyclohexane. The evidence for this statement which has always been quoted is the heats of combustion of the hydrocarbons, as measured by *Stohmann*; these values are probably not very accurate; they are shown in the following table together with the value for hexane. The table also gives the densities and boiling points of the hydrocarbons. As *Baeyer* pointed out (Ann. **278**, 115), the differences between these figures would be the same if the changes involved in the successive reductions were the same.

C_6H_6 (C.) = 779·8	(D.) = 68·2 kcal	b.p. 80·4°	d_{18} 0·8799,
C_6H_8 (C.) = 848·0	(D.) = 44·9 kcal	b.p. 83·5°	d_{20} 0·8478,
C_6H_{10} (C.) = 892·0	(D.) = 41·2 kcal	b.p. 80° or 86–87°	d_{20} 0·8102,
C_6H_{12} (C.) = 933·2	(D.) = 58·0 kcal	b.p. 81°	d_{20} 0·7788,
C_6H_{14} (C.) = 991·2		b.p. 69°	d_{20} 0·6603.

The special nature of benzene is shown more clearly by the more accurate and direct determinations of the heats of hydrogenation of unsaturated hydrocarbons by ***Kistiakowsky*** and his co-workers (Am. **57**, 65, 876; **58**, 137, 146; **59**, 831). The following table gives the heat effect on reduction of the first double bond of the compounds shown.

Cyclohexene H = — 28.59 kcal. per mol. (heat evolved)
Cyclohexadiene = — 26.76 „ „ „ „ „
Benzene = + 5.57 „ „ „ (heat absorbed)

Baeyers' strain theory (p. 7) was based on the idea that all the carbon atoms of an alicyclic compound lie in one plane. Theoretical considerations of models as well as experimental results have made it necessary to modify this view. It is held at present that only rings of five or less members are uniplanar, while rings of more members are arranged in three dimensions. The following are the most important reasons for this opinion:

The heat of combustion per methylene group for the cycloparaffins reaches a constant value with cyclohexane and cycloheptane, and is then equal to that of a methylene group in an open chain compound in which there can be no strain (cf. table p. 10; see also *Ruzicka*, Helv. **16**, 162).

Recent researches of *Ruzicka* (Helv. **9, 10, 11**) and of *Kerschbaum* (Ber. **60**, 902) into multi-membered cyclic ketones (p. 77) and lactones (I, 454), both natural and synthetic, have demonstrated a degree of stability for these large ring structures quite at variance with the predictions made by the classical strain theory.

The conceptions now generally adopted were first deduced by *Sachse* (Z. physik. Ch. **10**, 203; **11**, 185; Ber. **23**, 1365) from a consideration of the tetrahedral model and have been further developed by *Mohr* (J. pr. **98**, 349; Ber. **55**, 230; see also *Boeseken, Derx*, Rec. **39**, 183; **40**, 529; **41**, 327, 388). The carbon skeleton of cyclohexane is assumed to exist in two spatial modifications, represented by figs. (1) and (2) respectively. The four C-atoms 2, 3, 5 and 6 of both forms are arranged in one plane, while the two remaining C-atoms 1 and 4 are situated both on the same side of that plane in the "boat-form" fig. (1), and on opposite sides in the "chair form" fig. (2). One form can be transformed into the other by a slight perturbation, as the models indicate, and it can be shown that the energy required for this transformation is very small, much less than the excess of energy which the strain theory would predict on the assumption of a planar arrangement from the necessary deflection of valencies.

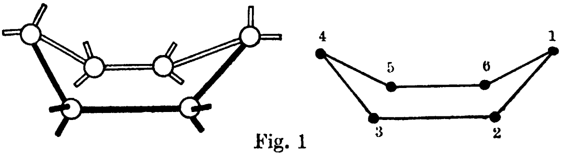


Fig. 1

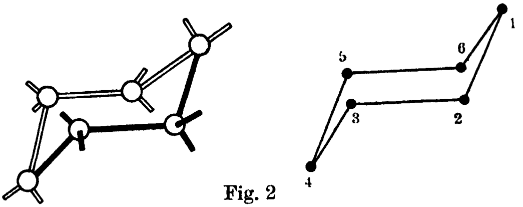
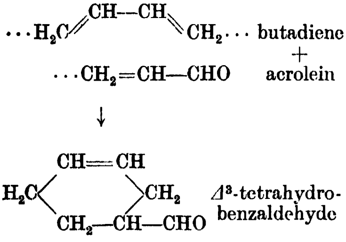
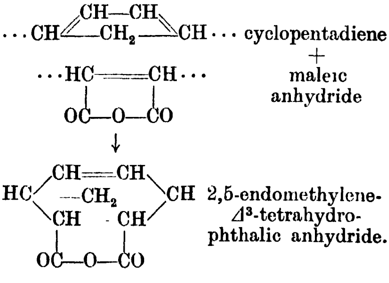


Fig. 2

The stereoisomerism of decalin (decahydronaphthalene, p. 171) discovered by *W. Huckel* (Ann. **441**, 42; **502**, 99) has nothing to do with *Sachse's* cyclohexane models, because both decalins can be deduced from either of *Sachse's* two forms. For cyclohexane itself the separate existence of a cis and a trans form has not been established and is very unlikely; claims have been made that this isomerism has been detected, but they have been disproved (*Linstead*, J. **1935**, 1063; *Goldschmidt*, Ber. **68**, 279). Among the various intermediate states between the boat form and the chair form of cyclohexane the plane form is never present, as an experimental investigation of the strain of bicyclo-heptane and bicyclo-octane indicates (*Bredt*, J. pr. **147**, 28). The high value of the parachor, + 8·2, as against + 6·1 with benzene, gives further support to the view of a three-dimensional arrangement of the cyclohexane ring (*Ray*, J. Ind. Chem. Soc. **12**, 764). Finally, recent researches into the fine structure of molecules, particularly the diagrams obtained by the diffraction of electrons (*Wierl*, Ann. Physik **8**, 521; *Mark*, Z. angew. Chem. **44**, 531; *Pauling*, *Brockway*, Am. **59**, 1228) give strong support to the *Sachse-Mohr* theory.

A most fruitful method of synthesising hydroaromatic compounds, known as the "*diene synthesis*", has been discovered by *Diels* and *Alder* (Ann. **460**, 98; **486**, 191 etc.); (cf. general methods of formation of cycloparaffins p. 21). The method can also be applied to multinuclear, bicyclic and heterocyclic compounds. It starts from hydrocarbons which contain two conjugated double bonds, that is to say from compounds derived from butadiene, $CH_2=CH-CH=CH_2$. These are combined with oxygen-containing compounds of the type $>C=CH-C=O$, which likewise contain a pair of conjugated double bonds. The simplest representative of this latter group is acrolein, $CH_2=CH-CHO$; maleic anhydride is often used. The reaction is one of simple addition but does not result in a molecular compound. Carbon atoms are linked together and quite new compounds are formed which may partially revert into the components. In most cases the reaction takes place at ordinary temperatures, not infrequently with development of heat, though the higher members of each series as a rule require to be heated more or less strongly. The course of the reaction appears to be as follows: the double bond between the carbons of the oxygen-containing reactant changes into a single bond, the free valencies of these atoms unite with the C-atoms in the terminal positions of the butadiene, the two double bonds of the butadiene are replaced by one double bond between the central atoms:





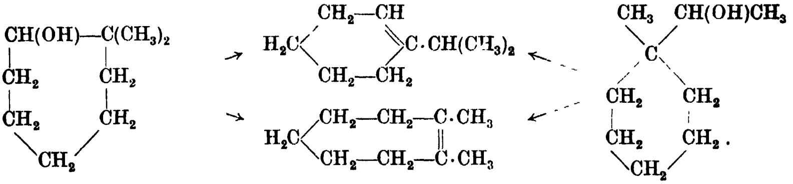
The reactants are thus linked to each other, as *Thiele's* ideas on addition in the 1,4-position would predict, without any shifting of the atoms. When the methylene group in cyclopentadiene is substituted by ethylene ($\Delta^{1,3}$-cyclohexadiene) or oxygen (furan) or by longer chains or rings, as e.g. in the phellandrenes (p. 211), *p*-endoethylene, *p*-endoxo- and similarly substituted compounds are formed by reactions analogous to the one shown. Patents on the subject are French Pat. 663,564, 672,025.

This diene synthesis, which perhaps can be compared with the *Grignard* synthesis for flexibility and scope, is regarded by the discoverers as of importance in the biological synthesis of many natural substances, especially of terpenes and alkaloids, because it occurs with such ease. In pure chemistry, apart from its synthetical value, it is very useful for elucidating doubtful processes which involve rearrangement and for confirming probable formulae.

The hydroaromatic compounds are characterised by their tendency to change into derivatives of five-membered rings. The change in the opposite direction does not take place so frequently (see Ring transitions p. 11). The former process has been studied especially in the action of potash on the dibromides of hexacarbocyclic ketones, in which the bromine atoms are attached to the carbon atom next to the CO group. It is not a question, as was formerly believed, of a benzilic acid rearrangement of 1,2-diketone formed as an intermediate product, but a more complicated process. A ketol is either formed as such or else a tautomer of the ketol, and in this compound the ring opens and an acid is formed which undergoes internal condensation to give a hydroxy acid with a five-membered ring. Thus, for example, in the conversion of 1,4-methyl-cyclohexanone into 1,3-methyl-cyclopentanone, 1-methyl-α-hydroxy-cyclopentane-3-carboxylic acid has been isolated as an intermediate product, and this acid probably occurs in several stereoisomeric forms. Corresponding hydroxy-cyclopentanone-carboxylic acids were also detected when 1,2-dimethyl-cyclohexanone-5 and 1,3,3-trimethyl-cyclohexanone-5 were converted into 1,3-dimethyl-cyclopentanone-4 and 1,3,3-trimethyl-cyclopentanone-5 respectively (*Wallach*, Ann. **414**, 296). For the theory of ring contraction see *Schenck*, J. pr. **134**, 215.

Similar ring contractions, and also ring enlargements from the five- to the six-membered ring, have been observed by *Meerwein* (Ann. **417**, 255) in the case of certain exocyclic alcohols. When he dehydrated 2,2-dimethyl-cyclohexanol-1 he observed the formation of 1,2-dimethyl-Δ^1-cyclohexene, which presupposes the migration of a methyl group, and also of Δ^1-isopropyl-cyclopentene. On the other hand, when 1-methyl-1,α-hydroxyethyl-cyclopentane (obtained from cyclopentanone by a number of steps) is dehydrated, 1,2-dimethyl-cyclohexene is practically the only product; with homologues of the former, the loss of water yields cyclopentene derivatives as well.

A very curious case of the mutual rearrangement of one ring system into another is that of 2,2-dimethyl-cycloheptanol-1 and 1-methyl-1,α-hydroxyethyl-cyclohexane. As *Meerwein* and *Schafer* (J. pr. **104**, 289) have shown, both these compounds when dehydrated by means of zinc chloride give the same two isomeric hydrocarbons, one containing a 6-ring, the other a 7-ring:



W. Huckel holds the view that in all ring rearrangements a strained ring changes into a strainless ring. The converse process has never been observed. *Nametkin* ("Die Umlagerung alicyclischer Kerne ineinander", Stuttgart 1926) formulates the following general conditions of ring transition: ring enlargement occurs only when the *side chain* of the alicyclic compound is attacked by the reagents used; ring contraction is observed when the attack is on the *nucleus*, and not on the side chain, under the conditions of reaction.

The action of free oxygen on unsaturated hydroaromatic compounds has been studied by *Wienhaus* (Angew. **41**, 617). In the main the double bonds remain intact, while a CH_2-group next to a double bond is attacked and an unsaturated alcohol or ketone is formed. The action of SeO_2 on cyclohexenes has been mentioned in the introduction (p. 16).

French authors often use the designations "cyclanes, cyclenes, cyclanols, cyclenols, cycloses, cyclanones, cyclenones" as group names for hexa- and tetra-hydrogenated 6-ring hydrocarbons, alcohols, inositols, ketones etc. These names have the advantage of brevity.

Thanks to the development of large-scale hydrogenation processes hydroaromatic compounds of all kinds are now easily available, and many are made commercially. They are widely used as solvents and plasticizers in the paint and lacquer industry and elsewhere, as motor fuel, as insecticides and as fixatives for perfumes, etc. *Schrauth* (Angew. **35**, 25) has given a survey of their manufacture and uses.

1. HYDROAROMATIC HYDROCARBONS

(a) Cyclohexanes, Hexahydrobenzenes ("Naphthenes")

Hydroaromatic hydrocarbons form a considerable fraction of Caucasian petroleum, the so-called naphtha (*Beilstein* and *Kurbatov*, Ber. **13**, 1818); *Markovnikov* therefore called them naphthenes. In addition to these hexahydrobenzenes, Caucasian petroleum also contains the isomeric alkylcyclopentanes (p. 47) (*Aschan*, Ber. **31**, 1803; Ann. **324**, 1; "Naphthenverbindungen", p. 1; *v. Braun*, Ann. **490**, 100). Cyclohexanes have also been discovered in petroleum from New Zealand and Borneo, in low-temperature coal tar, in lignite tar and shale tar, in rosin oil obtained by distilling colophony, and in acetone oil, the high-boiling fraction of crude acetone (*Easterfield*, Soc. Ch. Ind. **50**, 464; *Iimori*, Bull. Tokyo **1** (1928), 5, 8; *Pringsheim*, Angew. **40**, 1387). Finally, a "nonanaphthene", hexahydro-ψ-cumene, has been found in coal tar (*Ahrens*, Angew. **21**, 1411).

In the laboratory, the cyclohexanes are prepared from their halogen substitution products by reduction, or by interaction with alkyl-magnesium halides. They are obtained most easily by catalytic reduction of the benzene hydrocarbons or of cyclohexenes at ordinary or at higher temperatures (*Rosenmund*, Ber. **54**, 638, 1092; *Zelinsky*, Ber. **57**, 1066). If higher temperatures are used in the catalytic reduction of benzene homologues with fairly long side-chains, partial splitting off of the side chain occurs. Thus, from propyl-benzene small quantities of methyl- and ethyl-cyclohexanes are obtained besides propyl-cyclohexane. At temperatures above 300° cyclohexanes are decomposed by nickel, and H_2 and the corresponding benzene hydrocarbons are partially regenerated (*Sabatier*, C. r. **132**, 207, 631, 1254). This dehydrogenation of cyclohexanes to aromatic compounds can also carried out with Se, S, and metals such as Pt and Pd; the subject has been reviewed by *Linstead* (Ann. Reports Chem. Soc. **33** (1936), 294). Reduction of cyclohexanes to give open chain compounds does not take place at all readily (*Baeyer*, Ann. **278**, 88; cf. however *Kling*, Bull. **41** (1927), 1341).

When hydriodic acid is used as a reducing agent at an elevated temperature, alkyl-cyclopentanes are formed by a process of isomerisation. Thus, benzene gives methyl-cyclopentane as well as cyclohexane (*Markovnikov*, Ber. **30**, 1214; *Aschan*, Ann. **324**, 6).

The hexahydrobenzenes are distinguished from the isomeric olefins by their higher specific gravity and by their inability to take up bromine. Like the paraffins they react with chlorine or bromine to give monohalogen substitution products. When they are heated with dilute nitric acid, they are converted into nitro-substitution products; tertiary H-atoms are replaced by the NO_2 group more easily than others (*Markovnikov*, Ann. **301**, 154; **302**, 1; *Nametkin*, C. 1910 II 1376). With nitric and sulphuric acids small quantities of nitrated benzene hydrocarbons are produced.

When cyclohexane and its homologues are distilled with 20–30 per cent $AlCl_3$ at a temperature of 120–130°, only cyclohexane and methyl-cyclohexane remain unaffected. 1,2- and 1,4-Dimethyl-cyclohexane are converted into 1,3-dimethyl-cyclohexane. The higher members are decomposed into cyclohexene, which polymerises, and the paraffin hydrocarbon which corresponds to the aliphatic substituent. Amyl- and isoamyl-cyclohexane, e.g., give 70% and 42% respectively of n-butane, while the remainder consists of methane, tetramethyl- and pentamethyl-cyclohexane. It will be noticed that the side chains are broken up into methyl groups which can become re-attached to the nucleus (*Stratford*, Ann. Combustibles 4 (1929), 83). A general survey of the action of $AlCl_3$ on hydroaromatic compounds has been given by *Hopff*, Ber. **65**, 482; cf. also *Zelinsky*, ib. 1249; *Skita*, Angew. **45**, 286; *Turova-Pollak*, Ber. **68**, 1781.

When heated with $AlBr_3$ on a water bath cyclohexane gives 1,2-dimethylcyclobutane; methyl-cyclopentane is supposed to be the intermediate. The action of Br_2 and $AlBr_3$ converts the hexahydrobenzenes into substitution products of aromatic hydrocarbons.

According to the French Pat. 671,241 and the Brit. Pat. 327,411 a mixture of oily oxygenated products is obtained when cyclohexanes are heated with CO under pressure, or with acetyl chloride in the presence the halides of B or Al. Some of these have a pleasant odour.

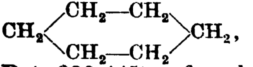
The simplest "naphthene", cyclohexane or hexahydrobenzene, is also called *hexanaphthene*, and its homologues *hepta-*, *octa-*, *nona-naphtenes*. It should be, however, remembered that in older literature these names have frequently been used for mixtures of hexa- and penta-carbocyclic hydrocarbons.

Cyclohexane, Hexahydrobenzene m.p. 6·54°		b.p. 80·3°/750 mm.[4]
Methylcyclohexane, Hexahydrotoluene m.p. — 126·3°		b.p. 100–100·2°/742 mm.[1]
1,1-Dimethylcyclohexane		b.p. 120°[4]
cis-**1,2-Dimethylcyclohexane**	Hexahydro-o-xylene	b.p. 126·5°/750 mm.[4]
trans-**1,2-Dimethylcyclohexane**		b.p. 124·5°/755 mm.[4]
cis-**1,3-Dimethylcyclohexane**	Hexahydro-m-xylene	b.p. 119°/756 mm.[4]
trans-**1,3-Dimethylcyclohexane**		b.p. 121·0°/760 mm.[4]
cis-**1,4-Dimethylcyclohexane**	Hexahydro-p-xylene	b.p. 120·5°/756 mm.[4]
trans-**1,4-Dimethylcyclohexane**		b.p. 119–119·5°/760 mm.[4]
Ethylcyclohexane m.p. — 128·9°		b.p. 129·5°/750 mm.[4]
cis-**1,2,3-Trimethylcyclohexane**	Hexahydro-hemimellithene	b.p. 144–146°/755 mm.[4]
trans-**1,2,3-Trimethylcyclohexane**		b.p. 142–146·5°/762 mm.[4]
cis-**1,2,4-Trimethylcyclohexane**	Hexahydro-ψ-cumene	b.p. 141·5°/760 mm.[4]
trans-**1,2,4-Trimethylcyclohexane**		b.p. 138·5-139·5°/755 mm.[4]
cis-**1,3,5-Trimethylcyclohexane**	Hexahydro-mesitylene	b.p. 140–140·5°/752 mm.[4]
trans-**1,3,5-Trimethylcyclohexane**		b.p. 138–139°/761 mm.[4]
1,2-Methylethylcyclohexane		b.p. 151°/750 mm.[4]
n-Propylcyclohexane m.p. — 94·5°[1]		b.p. 155°[3]
iso-**Propylcyclohexane** m.p. — 90·6°[1]		b.p. 154·7°/760 mm.[1]
1,2,3,4-Tetramethylcyclohexane		b.p. 84°/5 mm.[6]
cis-**1,2,4,5-Tetramethylcyclohexane**	Hexahydro-durene	b.p. 171°/755 mm.[4]
trans-**1,2,4,5-Tetramethylcyclohexane**		b.p. 169–170°/765 mm.[4]
cis-**1,3,4,5-Tetramethylcyclohexane**	Hexahydro-isodurene	b.p. 168–170°/762 mm.[4]
trans-**1,3,4,5-Tetramethylcyclohexane**		b.p. 162–164°/765 mm.[4]
1,3,5-Dimethylethylcyclohexane		b.p. 168·5–170°[5]
1,4-Methylisopropylcyclohexane, Hexahydrocymene		b.p. 167° (see Terpenes)
n-Butylcyclohexane m.p. — 78·6°[1]		b.p. 177°[3]
Isobutylcyclohexane		b.p. 169°/754 mm.[4]
sec. **Butylcyclohexane**		b.p. 177·2°/760 mm.[1]
tert. **Butylcyclohexane**		b.p. 167–169°[2]
1,3-Diethylcyclohexane		b.p. 169–173°[2]
Amylcyclohexane		b.p. 199°[3]
Hexylcyclohexane		b.p. 221°[3]

References: (1) *Timmermans*, Belg. **36** (1927), 502. (2) *Stratford*, Ann. comb. **4** (1929), 83. (3) *Bourguel*, Bull. **41** (1927), 1475. (4) *Eisenlohr*, C. 1926 I 75. (5) *Markovnikov*, C. 1899 I 176. (6) *Mitchell*, Am. **55**, 4278.

Of these hydrocarbons, cyclohexane, methyl-, 1,3-dimethyl-, 1,3,4-trimethyl- and 1,3,5-dimethyl-ethyl-cyclohexane have been found in the naphtha of Caucasian petroleum, while cyclohexane, methyl-cyclohexane and probably a dimethyl-cyclohexane occur in New Zealand petroleum (*Markovnikov*, Ber. **28**, 1234; Ann. **302**, 2; *Easterfield*, Chem. Ind. **1** (1923), 936).

Methyl-, propyl-, 1,3-dimethyl- and 1,4-methyl-isopropyl-cyclohexane have been found in rosin oil. Most of the compounds listed in the table have been prepared by reduction of the corresponding benzene derivatives by the methods described above.

Cyclohexane, *hexahydrobenzene, hexamethylene, "naphthene",*  $CH_2\left\langle\begin{matrix}CH_2-CH_2\\CH_2-CH_2\end{matrix}\right\rangle CH_2$, results from the reduction of benzene (Brit. Pat. 322,445), of cyclohexene and of cyclohexadiene (*Zelinsky,* Ber. **57**, 1066), from the catalytic reduction of cyclohexanol (*Kling,* Bull. **41** (1926), 1341) or by the action of sodium on synthetic 1,6-dibromohexane. Small amounts of cyclohexane are formed when n-hexane is boiled with moist $AlCl_3$ (*Nenitzescu,* Ber. **66**, 1895). Pure cyclohexane is a liquid smelling like petroleum ether. Heated with bromine to 150°, it yields 1,2,4,5-tetrabromo-benzene; hot nitric acid oxidises it to adipic acid (*Aschan,* Ann. **324**, 3). Cyclohexane can be separated from benzene by adding certain solvents, e.g. ethylene chlorohydrin or glycol monoacetate (Brit. Pat. 324,350). At a temperature of 700–800° it decomposes, giving some butadiene (*Frolich,* Ind. Eng. **22**, 240). When it is heated to 500–510° in presence of Al_2O_3 and under a pressure of 100–120 atm., methylcyclopentane and benzene hydrocarbons are formed (*Ipatiev,* Ber. **44**, 2987; *Ando,* J. Chem. Soc. Japan **35** (1932), 455; **36** (1933), 396). Lead and tin compounds of cyclohexane have been prepared by *Grüttner* (Ber. **47**, 3257) and *Krause* (Ber. **57**, 532) from cyclohexyl-Mg-halides and the corresponding metal halides. *Zelinsky* (Ber. **65**, 1249; Ann. **508**, 115) and *Nenitzescu* (Ber. **66**, 969, 1097; **69**, 1040) have studied the reaction with $AlCl_3$ under varying conditions, with and without acetyl chloride. Fuming sulphuric acid converts it at ordinary temperatures into benzene sulphonic acid with a yield of 70% (*Menschutkin,* C. 1930 II 1541).

Methyl-cyclohexane, *hexahydrotoluene, "heptanaphthene",* has been obtained by the catalytic reduction of toluene or of a mixture of benzene and methane, from cycloheptanol (p. 71) by the action of HI at 140° (*Markovnikov,* C. r. **114**, 1068), and also from synthetic methyl-cyclohexanone through the corresponding alcohol (*Zelinsky,* Ber. **29**, 731). Bromine and $AlBr_3$ convert it into *pentabromo-toluene,* m.p. 282°.

1,1-Dimethyl-cyclohexane, b.p. 119·8°, is formed from 1,1-dimethyl-dihydroresorcinol through the steps of the chloride and the alcohol, or from acetyl-methyl-heptenone by means of 80% H_2SO_4 (*Crossley,* J. **87**, 1487; **119**, 271); it is best prepared by hydrogenation of dimethyl-dihydroresorcinol on active Pt (*Miller,* Belg. **44** (1935), 513). On catalytic dehydrogenation this compound does not behave in the normal way; unlike its isomers it remains unchanged (*Zelinsky,* Ber. **56**, 1716). This is scarcely surprising, since there are two methyl groups attached to one carbon atom, and an aromatic compound cannot be formed unless one of these is lost.

The trans forms of the three other dimethyl-cyclohexanes are formed when the corresponding xylenes are hydrogenated on Ni. When colloidal Pt or Pt-black are used, a greater proportion of the cis forms is obtained (*Zelinsky,* Ber. **65**, 1613). For the thermal decomposition of the three dimethylcyclohexanes see *Arbuzov,* C. 1936 II 1156.

1,2-Dimethylcyclohexane has been found in Galician petroleum (*Skovronski,* C. 1919 IV 586). **1,3-Dimethylcyclohexane,** *hexahydro-m-xylene, "octanaphthene",* is obtained from camphoric acid and from Me-cyclohexane-carboxylic acid by means of HI (*Lossen,* Ann. **225**, 10; *Aschan,* Ber. **24**, 2718; *Wallach,* ib. **25**, 920; *Balbiano,* Gazz. **35**, I, 144); also from 2,6-dimethylcyclohexanol. This substance has been obtained in a feebly dextrorotatory form, $[\alpha]_D$ + 0·8°, from optically active 1,3-dimethyl-cyclohexanol. **1,4-Dimethylcyclohexane** has been made synthetically from dimethyl-succino-succinic ester (*Zelinsky*, Ber. **31**, 3206; **35**, 2680). **Ethylcyclohexane** is obtained from acetophenone by reduction on a Pt-Fe catalyst, together with cyclohexyl carbinol and hexahydro-acetophenone (p. 124), also from ethyl-benzene on a Pt-PtO$_2$ catalyst (*Faillebin*, Ann. ch. (10), **4**, 156, 410; *van Woerden*, Rec. **45**, 124; *Adams*, Am. **50**, 1970). For the preparation of mono- and di-alkyl cyclohexanes see *Signaigo*, Am. **55**, 3326.

1,3,4-Trimethylcyclohexane, *hexahydro-pseudocumene*, "*nonanaphthene*", from 2,3,6-trimethyl-cyclohexanol (*Zelinsky*, Ber. **29**, 215), reacts with Br$_2$ and AlBr$_3$ to give tribromo-ψ-cumene. **n-Propylcyclohexane** has been synthesised from chloro-cyclohexane, propyl iodide and zinc (*Kurssanov*, Ber. **34**, 2035).

1,3-Methyl-isopropyl-cyclohexane, *m-menthane*, b.p. 167°, is formed by reduction of its iodine substitution product. **1,4-Methyl-isopropyl-cyclohexane,** *p-menthane*, see p. 215. **1,3-Diethyl-cyclohexane,** b.p. 170°, d$_{22}$ 0·7957, is obtained from 2,6-diethyl-cyclohexanol. **Phenylcyclohexane,** m.p. 7°, b.p. 107°/13 mm., is obtained from cyclohexyl chloride, benzene and AlCl$_3$ (*Neunhöffer*, J. pr. **133**, 95).

1,2-Dibenzhydryl-cyclohexane, $C_{32}H_{32}$, cis m.p. 174–175°, trans m.p. 210–212°, can be prepared from the dimethyl-ether of 1,2-bis-(diphenyl-hydroxymethyl)-cyclohexane, and also from 1,1,8,8-tetraphenyl-octadiene-1,7 (*Wittig*, Ber. **67**, 667).

Halogen Substitution Products of the Cyclohexanes. — *Methods of formation*: (1) From the cyclohexanes by the direct action of a halogen. (2) By the addition of halogens or hydrogen halides to di- and tetra-hydrobenzenes. (3) By the addition of halogens to benzenes and halogenated benzenes (vol. III). (4) From cyclohexanols through the exchange of hydroxyl groups for halogen by means of H-halides or P-halides (*van Woerden*, Rec. **45**, 124). (5) From cyclohexyl ethers with fuming halogen acids and red phosphorus in a sealed tube at 200° (*Lacourt*, Belg. **36**, 346).

The third method has brought to light some characteristic examples of isomerism. Two isomeric benzene hexachlorides, and two isomeric chlorobenzene hexachlorides have been found. This isomerism is geometrical and arises from the different positions of the halogen atoms which are added on with respect to the plane of the carbon ring, as with the isomeric trithioaldehydes (I 246) and the isomeric cyclopropane, cyclobutane and cyclopentane dicarboxylic acids (p. 30, 39, 63).

Cis and trans forms of of the dihalogen cyclohexanes and the monohalogen alkylcyclohexanes have also been obtained.

Fluoro-cyclohexane	m.p. 13°	b.p. 100·2°
Chloro-cyclohexane		b.p. 142·9°/760 mm.
Bromo-cyclohexane		b.p. 52·5°/13·5 mm.
Iodo-cyclohexane		b.p. 70–73°/13 mm.
1,1-Methylchloro-cyclohexane		b.p. 54°/40 mm.
1,2-Methylchloro-cyclohexane		b.p. 43·5–44°/13 mm.
1,3-Methylchloro-cyclohexane		b.p. 160°
1,4-Methylchloro-cyclohexane		b.p. 47·0–47·5°/13·5 mm.
1,2-Methylbromo-cyclohexane		b.p. 62–63°/18 mm.
1,3-Methylbromo-cyclohexane		b.p. 60–71°/10 mm. depending on preparation
1,4-Methylbromo-cyclohexane		b.p. 68°/20 mm.
1,2-Methyliodo-cyclohexane		b.p. 97°/30 mm.
1,3-Methyliodo-cyclohexane		b.p. 61–63°/3 mm.
1,4-Methyliodo-cyclohexane		b.p. 63°/3·5 mm.
1,2-Dichloro-cyclohexane		b.p. 190°/760 mm.

1,2-Dibromo-cyclohexane	b.p. 96°/8 mm.
1,3-Dibromo-cyclohexane	m.p. 11°
cis-1,4-Dibromo-cyclohexane	m.p. 48°
trans-1,4-Dibromo-cyclohexane	m.p. 112°

In addition to monochloro-cyclohexane, various **di-, tri-** and **tetrachloro-cyclohexanes** have been obtained by chlorinating cyclohexane at 0°. With KOH they yield cyclohexene, chloro-cyclohexene, chloro-hexadiene, benzene, and chloro-benzene (*Sabatier*, C. r. **137**, 240).

Unlike the alkyl halides, the halogen derivatives of the cyclohexanes cannot be converted into the corresponding alcohols, cyanides, mercaptans etc. by the action of alkalies or other compounds of an alkaline reaction, such as KCN, KSH, Ag_2O, NH_3, sodio-malonic ester etc. With such reagents hydrogen halide is lost, and a cyclohexene or cyclohexadiene is formed (see *Foragher*, Am. **43**, 1715; *Tronov, Ladigina*, Ber. **63**, 3060; *King*, J. **1935**, 982). On the other hand, the cyclohexyl magnesium halides can be readily prepared (preparation: *Gilman*, Am. **53**, 1945) and can be converted by oxygen into the alcohols, and by CO_2 into the carboxylic acids; they react with aldehydes and ketones to give exocyclic alcohols. When the vapours of halogenated cyclohexanes are passed over hot alumina, hydrogen halide is split off with ease and cyclohexenes are formed.

Cyclohexyl-silicon trichloride, $C_6H_{11}SiCl_3$, b.p. 208–211°, is obtained from cyclohexyl-Mg-chloride and $SiCl_4$ (*Palmer*, J. **1930**, 1020).

α- or trans **Benzene hexachloride,** $C_6H_6Cl_6$, melts at 157° and boils at 218°/345 mm. with decomposition into 3 HCl and 1,2,4-trichloro-benzene (vol. III). β- or cis **Benzene hexachloride,** m. and sublim. p. circ. 310°; is obtained by the action of chlorine upon benzene in sunlight (*Faraday* 1825; *Mitscherlich* 1835). Both compounds are produced when chlorine is led into boiling benzene (*Meunier* 1884) or, better, into a mixture of benzene and 1% NaOH. The α-compound is separated by steam from the less volatile β-derivative (*Matthews*, J. **59**, 165), or by means of chloroform from the less soluble β-isomer. The latter is the more stable of the two modifications. When heated with alcoholic potash it is converted into 1,2,4-trichloro-benzene with greater difficulty than the α-compound. It is not affected by alcoholic KCN, while the α-isomer, when boiled with this reagent, gives trichloro-benzene. Zinc in EtOH solution converts the α-modification into benzene (*Zinin*, Ztschr. f. Chem. (N. F.) 7 (1871), 284, 293).

α- and β-**Chloro-benzene hexachlorides,** $C_6H_5Cl_7$, m.ps. 146° and 260°, yield 1,2,3,5-tetrachloro-benzene with alcoholic potash (*Otto*, Ann. **141**, 101).
1,2,4-Trichloro-benzene-hexachloride, $C_6H_3Cl_9$, melts at 95°.

o-Xylene hexachloride, $C_6H_4(Me)_2Cl_6$, m.p. 194°, b.p. 260–265° (*Radziwanovski*, C. 1898 I 1010).

Benzene hexabromide, $C_6H_6Br_6$, α-form m.p. 212°, β-form m.p. 253°, results from the action of Br_2 upon benzene in sunlight or on heating. Both forms split off HBr to form 1,2,4-tribromo-benzene (*Mitscherlich*, l. c.). The α-form is isomorphous with α-benzene hexachloride (*Meunier*, C. r. **101**, 378; *Matthews*, J. **73**, 243).

(b) Cyclohexenes, Tetrahydrobenzenes ("Naphthylenes")

A tetrahydrotoluene has been discovered in low-temperature tar from East Indian coal, and also, together with methylcyclohexane and allied hydrocarbons, in rosin spirit (*Rassow* et al., C. 1926 II 2648).

Cyclohexenes are produced in the laboratory: (1) from halogenated cyclohexanes by elimination of hydrogen halide by means of alkali, alkali carbonate, acetate or phenate, or of tertiary amines, especially quinoline; (2) from amino-cyclohexanes by dry distillation of their hydrochlorides or phosphates; (3) from the cyclohexanols by dehydration with $KHSO_4$, P_2O_5, dilute H_2SO_4, $ZnCl_2$, $AlCl_3$ or by heating with aqueous oxalic acid (*Zelinsky*, Ber. **34**, 3249) or phthalic anhydride, or by catalytic dehydration (*Inoue*, Bull. Chem. Soc. Japan 1 (1926), 219; *Lacourt*, Belg. **36**, 346); tertiary alcohols, obtained from cyclic ketones and *Grignard* reagents, lose water on heating.

A very mild method of preparing cyclohexenes from cyclohexanols which eliminates any danger of isomerisation is that discovered by *Tchugaev* (Ber. **32**, 3332). The Na or K salts of the cyclohexanols are converted by the action of CS_2 into xanthates; these on methylation give the corresponding methyl-xanthates, which, when distilled at ordinary pressure, decompose into COS, methyl-mercaptan and the corresponding cyclohexene:

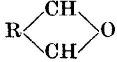
$$C_nH_{2n-1}O \cdot CS \cdot SMe = C_nH_{2n-2} + COS + MeSH.$$

This method is particularly suitable for the higher alcohols, and has been most useful for preparing terpenes. The alkylidene-cyclohexanes which contain a *semicyclic double bond*, such as methylene-, or ethylidene- etc. cyclohexanes, are isomeric with the alkyl-cyclohexenes. These hydrocarbons, which are of special importance in the chemistry of terpenes, are obtained by removal of CO_2 from the cyclohexene and cyclohexylidene fatty acids (p. 133) prepared by the condensation of cyclohexanones with bromo-aliphatic esters and zinc, followed by hydrolysis and dehydration. They differ from the isomeric cyclohexenes in which the double bond is in the ring by their higher specific gravities, higher boiling points and abnormal molecular refractions (*Wallach*, Ann. **360**, 36; *Auwers*, ib. **410**, 287). They have a higher energy content than their endocyclic-unsaturated isomers:

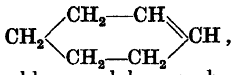
$$C_6H_{10}:CH_2 = C_6H_9 \cdot Me + 21\ \text{kcal};\quad C_6H_{10}:CHMe = C_6H_9 \cdot CH_2 \cdot Me + 20\ \text{kcal}$$

(*Roth*, Z. Elektroch. **17** (1911), 793). On heating with alcoholic sulphuric acid the double bond readily migrates and true cyclohexenes result.

A similar capacity of isomeric change is shown to some extent by all cyclohexenes, especially under the influence of acids, so that the preparation of a perfectly homogeneous hydrocarbon, with the obvious exception of cyclohexene itself, has probably not yet been accomplished. In general, a cyclic double bond will only go over to the semicyclic position when a conjugated system is set up by the migration (*W. Huckel.* "Der gegenwartige Stand der Spannungstheorie", Berlin 1927).

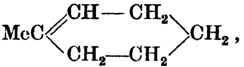
The cyclohexenes are characterised by their great reactivity. They add on NOCl, N_2O_3 and N_2O_4 to form nitrosochlorides, nitrosites and nitrosates (cf. Terpenes). When treated with benzoyl peroxide they give cyclohexene oxides  $R\Big\langle\begin{matrix}CH\\ CH\end{matrix}\Big\rangle O$, which take up water to form 1,2-cyclohexane-diols (*Nametkin*, Ber. **56**, 1803). Some cyclohexenes unite with phenol in the presence of glacial acetic and sulphuric acids to give cyclohexyl-phenol; e.g. the three methyl-cyclohexenes give the same-p-methyl-cyclohexyl-phenol, m.p. 112·5° (*Schrauth*, Ber. **57**, 854). The vapours of cyclohexenes, when heated in the presence of Pd-asbestos as a catalyst, decompose into aromatic hydrocarbons and cyclohexanes (see above) (*Zelinsky*, Ber. **57**, 1066). For the separation of these reaction products see p. 90.

Cyclohexene, *Tetrahydrobenzene*	m.p. – 103·7°	b.p. 83·5°
Δ^1-Methylcyclohexene		b.p. 110–111°
Δ^2-Methylcyclohexene		b.p. 104–105°
Δ^3-Methylcyclohexene		b.p. 102–102·7°
Methylene-cyclohexane		b.p. 102·5°
1,2-Dimethylcyclohexene-1		b.p. 135–137°
1,4-Dimethylcyclohexene-1		b.p. 127–128°
2,4-Dimethylcyclohexene-1		b.p. 127–128°
3,5-Dimethylcyclohexene-1		b.p. 126–127°
4,6-Dimethylcyclohexene-1		b.p. 126–127°
1-Methyl-4-methylene-cyclohexane		b.p. 122°
Ethylidene-cyclohexane		b.p. 136–136·4°
1,3,5-Trimethylcyclohexene-1		b.p. 139–141°
1,3-Dimethyl-5-methylene-cyclohexane		b.p. 135–136°
Ethyl-4-methylcyclohexene-1		b.p. 153–154°
1-Propylcyclohexene-1		b.p. 155–156°

Cyclohexene, tetrahydrobenzene,  $\mathrm{CH_2}<\begin{matrix}\mathrm{CH_2-CH}\\ \mathrm{CH_2-CH_2}\end{matrix}\gg\mathrm{CH}$, b.p. 83·5°, is obtained from monobromo- or monochloro-cyclohexane by heating with quinoline or alcoholic potash (*Markovnikov*, Ann. **302**, 27), from 1,4-dibromo-cyclohexane with Na, together with cyclohexadiene (*Prjanishnikov*, Ber. **67**, 64), and from cyclohexanol by heating with oxalic acid (*Zelinsky*, Ber. **34**, 3252) or $SOCl_2$ (*Carré*, Bull. **3** (1936), 144), or $KHSO_4$ (*Brunel*, Bull. **33** (1905), 270), or by catalytic dehydration (*Inoue*, Bull. Japan **1** (1926), 219). It is a colourless liquid. It smells like kerosene and not of leeks, as does cyclohexadiene. It gives a yellow colour with conc. sulphuric acid. With aliphatic acid chlorides and $AlCl_3$ it yields acyl-cyclohexenes, e.g.: with acetyl chloride: Δ^1-tetrahydro-acetophenone together with 2-chloro-hexahydro-acetophenone (*Wieland*, Ber. **55**, 2246); with n-butyryl chloride: n-butyryl-cyclohexene (*Darzens*, C. r. **151**, 758). It forms a very stable *ozonide* $C_6H_{10}O_3$, m.p. 75°, which can be recrystallised from EtOH, but is decomposed by water with formation of adipic dialdehyde and adipic acid (*Harries*, Ber. **42**, 694; *Fischer*, Ber. **65**, 1471). *Nitrosochloride* m.p. 152° (*Wallach*, Ann. **343**, 49). *Pseudonitrosite* m.p. 145° dec.

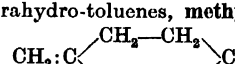
According to *Zelinsky* (Ber. **63**, 2362) the autoxidation of cyclohexene at ordinary temperatures yields a reddish resinous mass which contains some cyclohexene peroxide. If the oxidation is carried out in the presence of Os salts, cyclohexanol is found among the products (*Kotz*, J. pr. **111**, 373).

Methylcyclohexenes, tetrahydrotoluenes, $C_6H_9\cdot Me$. Three methyl-cyclohexenes are possible, the isomerism depending upon the position of the double linkage.

Δ^1-Methylcyclohexene,  $\mathrm{MeC}\ll\begin{matrix}\mathrm{CH-CH_2}\\ \mathrm{CH_2-CH_2}\end{matrix}>\mathrm{CH_2}$, b.p. 110–111°, d_{17} 0·799, is the most stable of the three and is easily obtained from its isomers by a shift of the double bond. It is formed, nearly pure, from 1,1- and 1,2-methyl-cyclohexanols by elimination of water. *Wallach* also found that it is present in the mixture of hydrocarbons obtained by treating 1,3- and 1,4-methyl-cyclohexanols with P_2O_5 or $ZnCl_2$. He identified it by its *nitrol-piperidide* $C_7H_{12}(NO)NC_5H_{10}$, m.p. 153°, and by oxidising it to δ-acetyl-valeric acid (Ann. **359**, 287).

Markovnikov obtained what seems to be a fairly homogeneous **Δ^3-methyl-cyclohexene,** b.p. 102–102·7°, d_{15} 0·841, $[\alpha]_D + 110°$, by heating the phthalic mono-ester or the methyl-xanthate of the optically active 1,3-methyl-cyclohexanol; it is also obtained by dehydration of 1,4-methylcyclohexanol (*Dupont*, Bull. Belg. **45**, 57). On oxidation with $KMnO_4$ it yields β-methyl-adipic acid (*Markovnikov*, C. 1904 I 1213, 1346). **Δ^2-Methylcyclohexene,** b.p. 104–105°, d_{27} 0·7937, $[\alpha]_D + 81·47°$, is obtained from 1-methyl-3-iodo-cyclohexane (*Zelinsky*, Ber. **34**, 3252; **35**, 2493). A methyl-cyclohexene has been obtained synthetically from perseitol (I 681) by heating with HI (*Maquenne*, C. r. **114**, 1066).

An isomer of the tetrahydro-toluenes, **methylene-cyclohexane,**



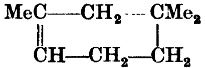
$$\mathrm{CH_2{:}C}<\begin{matrix}\mathrm{CH_2-CH_2}\\ \mathrm{CH_2-CH_2}\end{matrix}>\mathrm{CH_2}$$

b.p. 102·5°, $d_4^{17\cdot 6}$ 0·8036, $n_{D_{17\cdot 80}}$ 1·45092, is obtained from cyclohexylidene-acetic acid (p. 134), and from hexahydrobenzyl iodide with alcoholic potash (*Wallach*, Ann. **359**, 291; *Favorsky*, Ber. **40**, 4863). On oxidation with $KMnO_4$ it yields cyclohexanone and a *glycol*, $C_7H_{12}(OH)_2$, m.p. 77°, which, on heating with dilute H_2SO_4, is converted into hexahydrobenzaldehyde. When boiled with alcoholic sulphuric acid, it is converted into the isomeric Δ^1-methyl-cyclohexene. *Nitrol-piperidide* m.p. 127°.

Several homologous tetrahydrobenzenes have been obtained, mostly by elimination of water from the corresponding cyclohexanols. Their homogeneity is doubtful, as has been stated. **1,2-Dimethylcyclohexene-1,** b.p. 135–137°, *nitrosochloride* m.p. 88°, is also formed from 2,2-dimethyl-cyclohexanol, by dehydration and migration of a methyl group (reversal of the pinacolin transformation, I 363), together with 2-isopropyl-Δ^2-cyclopentenone-1; it readily gives a crystalline *dibromide,* m.p. 154–156° (*Meerwein,* Ann. **405,** 147). **1,3-Dimethylcyclohexene-1,** b.p. 124°, **1,4-dimethylcyclohexene-1,** b.p. 124–126°/751 mm. (*Zelinsky,* Ber. **41,** 2632; *Auwers,* Ann. **410,** 267). **2,2-Dimethylcyclohexene-1,** b.p. 117°, from dimethyl-dihydroresorcinol, gives α,α-dimethyl-adipic acid on oxidation with $KMnO_4$ (*Crossley,* J. **89,** 1554). **1,5-Dimethylcyclohexene-1,** b.p. 124–126°/760 mm., is obtained from methyl-heptenone with P_2O_5 or $ZnCl_2$ (*Wallach,* Ann. **395,** 80). **3,5-Dimethylcyclohexene-1,** b.p. 126–127°/746 mm. (*Auwers,* Ann. **410,** 267). **1-Methyl-4-methylene-cyclohexane,** b.p. 122°. **1,3,5-Trimethyl-cyclohexene-1,** b.p. 139–141°/766 mm., *nitrosochloride* m.p. 134° (ib.). **1,3-Dimethyl-5-methylene-cyclohexane,** b.p. 135–136°/744 mm. **4-Methyl-4-ethyl-cyclohexene-1,** b.p. 153–154°, *nitrosochloride,* m.p. 103–104° and 98–99°. **Δ^1-Ethyl-, -propyl- and -isopropylcyclohexenes** boil at 135°, 155° and 156° resp.; they are formed by isomeric change from **ethylidene-, propylidene- and isopropylidene-cyclohexanes,** b.pp. 136°, 158° and 161° (*Wallach,* Ann. **360,** 44). **Allyl-cyclohexane,** $C_6H_{11}CH{\cdot}CH{:}CH_2$, b.p. 149°, from cyclohexyl-Mg bromide and allyl bromide (*Rességuier,* Bull. 7 (1910), 431).

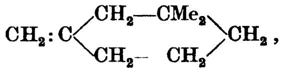
For stereoisomeric tri- and tetramethyl-cyclohexenes see *Skita,* Ber. **55,** 151; cyclohexyl-propene, -butene, -pentene etc. see *Bourguel,* Bull. **41** (1927), 1475.

Δ^1-1,5,5-Trimethyl-cyclohexene, *α-cyclogeraniolene,*



b.p. 139–141°, is obtained from the unsaturated terpene geraniolene (p. 207) by treating it with sulphuric acid, together with the isomeric *β-cyclogeraniolene.* It is also formed from synthetic *dimethyl-heptenol,* $Me_2C(OH){\cdot}CH_2CH_2CH{:}CM_2$, by boiling with phosphoric acid (*Harries,* Ber. **37,** 848) and by the action of zinc chloride upon dihydro-isoacetophorol (3,5,5-trimethyl-cyclohexanol) (p. 110); it yields a sparingly soluble nitrosochloride and nitrosate (*Wallach,* Ann. **324,** 97, 112).

1-Methylene-3,3-dimethyl-cyclohexane, *γ-cyclogeraniolene,*



b.p. 138–141°/739 mm., is obtained from dimethyl-heptenol and oxalic acid at 140–150°. Methyl- and ethyl-γ-cyclogeraniolenes (1-methylene-2-alkyl-3,3-dimethyl-cyclohexanes) are prepared similarly from dimethyl-octenol, dimethyl-nonenol and homologues (*Escourrou,* Bull. **39** (1926), 1460).

For **allyl-cyclohexenes** and **cyclohexene-all(yl)ene** see *Tiffeneau,* C. r. **202,** 1931.

1-Methyl-3-allyl-Δ^3-cyclohexene, $C_6H_8Me(1)C_3H_5(3)$, b.p. 171–173°, is prepared from 1-methyl-3-allyl-cyclohexane-3-ol by way of the chloride (*Zaicev,* J. **110** I 267). **1-Phenyl-Δ^1-cyclohexene,** b.p. 136–138°/25 mm. (*Noller, Kaneko,* Am. **57,** 2442). **1-Benzyl-Δ^1-cyclohexene,** b.p. 125°/11·5 mm., from 1-benzyl-cyclohexanol-2 or from cyclohexyl-phenyl-carbinol by removal of water (*Auwers,* Ber. **68,** 2174). **2-Benzyl-Δ^1-cyclohexene,** b.p. 127·2–128·4°/15 mm. is formed from cyclohexene and benzyl alcohol with P_2O_5 (*Kurssanov.* C. 1931 I 3112).

Special interest attaches to the Δ^1- and Δ^3-1,4-methyl-isopropyl-cyclohexenes, *carvomenthene* and *menthene,* which are closely related to the terpenes, and are therefore dealt with in that section.

γ-Carotene, $C_{40}H_{56}$, a monocyclic polyene hydrocarbon, a complicated cyclohexene derivative, is dealt with on p. 412.

(c) Cyclohexadienes, Dihydrobenzenes

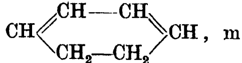
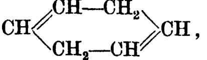
The natural *monocyclic terpenes* belong to the dihydrobenzene group; they can be regarded as dihydro-p-cymenes. The artificially prepared dihydrobenzenes resemble them closely in behaviour.

The method of preparing the simplest of the hydrocarbons in this class, dihydrobenzene, from succino-succinic ester has already been discussed (p. 83). Monoalkyl and p-di-alkyl-dihydrobenzenes have been obtained similarly from mono- and di-alkyl succino-succinic esters (*Baeyer*, Ber. **26**, 232). 1,2,3,5-Tetramethyl-dihydrobenzene probably occurs in amber oil, since 1,3-dimethyl-terephthalic acid is found among its oxidation products.

The other methods of preparing cyclohexadienes are completely analogous to those employed for cyclohexanes. They are formed (1) from the cyclohexanediols, many of which can be obtained by reducing the dihydro-resorcinols, which can be readily synthesised (p. 112), and also from the cyclohexenols, by dehydration; (2) from the dibromides of the cyclohexenes by heating with quinoline (cp. *Harries*, Ber. **42**, 693); (3) by distillation of the phosphates of diamino-cyclohexanes in a current of CO_2, under reduced pressure if necessary (id. Ann. **328**, 88; *Crossley*, J. **95**, 930).

Most of the dihydrobenzenes have a penetrating odour like that of leek. They polymerise and resinify easily. With alcoholic sulphuric acid, or with $Ac_2O + H_2SO_4$, they give characteristic red or purple colours. With hydrogen halides they yield halogenated tetrahydrobenzenes. They can usually be converted with ease into benzene derivatives by oxidising agents.

In many dihydrobenzenes the position of the double bonds is still doubtful, and some of these substances may be mixtures. Recently, however, methods have been worked out to obtain homogeneous hydrocarbons. Measurements of the molecular refraction have been used as evidence for the constitution of dihydrobenzenes (*Auwers*, Ber. **43**, 3076).

$\Delta^{1,3}$-Cyclohexadiene, dihydrobenzene,  $CH\left\langle\begin{array}{c}CH{-}CH\\CH_2{-}CH_2\end{array}\right\rangle CH$, m.p. –95°, b.p. 80–80·5°, has been obtained: from 1,3-diamino-cyclohexyl phosphate by distillation; together with cyclohexene, from 1,4-dibromo-cyclohexane with Na (*Prjashnishnikov*, Ber. **67**, 64); and from 1,3-dichloro- or 1,2-dibromo-cyclohexanes on heating with trimethylamine in a sealed tube, or with quinoline, when a little cyclohexene and small quantities of the isomeric **$\Delta^{1,4}$-cyclohexadiene,**  $CH\left\langle\begin{array}{c}CH{-}CH_2\\CH_2{-}CH\end{array}\right\rangle CH$, b.p. 86–87°, are formed as by-products; the latter is obtained from 1,4-diamino-cyclohexane as the main product. 1,2-Dibromo-cyclohexane with NaOEt gives 20–30% of $\Delta^{1,3}$-dihydrobenzene, and 50–60% of 1-ethoxy-Δ^2-tetrahydrobenzene, b.p. 154–155°; the latter with $KHSO_4$ at 170° gives an additional quantity of $\Delta^{1,3}$-dihydrobenzene (*Hofmann*, C. 1926 I 2342). 1,4-Dibromo-cyclohexane gives a mixture of the two isomeric dihydrobenzenes (*Harries* and *Antoni*, Ann. **328**, 105; *Zelinsky*, Ber. **41**, 2479; *Harries*, Ber. **42**, 693; *Crossley*, J. **83**, 1403). The $\Delta^{1,4}$-isomer has also been prepared from the diols resorcitol and quinitol (p. 102) by dehydration with dilute H_2SO_4 (*Senderens*, C. r. **177**, 1183).

1,4-Cyclohexadiene readily gives a *tetrabromide*, m.p. 188°, while 1,3-cyclohexadiene yields at first a *dibromide*, m.p. 109°, probably 1,4-dibromo-Δ^2-cyclohexene, as the principal product; this latter on heating with quinoline is converted into benzene, and on treatment with more bromine gives a **tetrabromo-cyclohexane,** m.p. 87–88°.

$\Delta^{1,3}$-Dihydrobenzene has been used by *Diels* and *Alder* in many diene syntheses (p. 86) (Ann. **460**, 115; **478**, 138; **490**, 241; **501**, 9). For a dimeric 1,3-cyclohexadiene see *Alder*, Ann. **496**, 197, and p. 193. For the oxidation of $\Delta^{1,4}$-dihydrobenzene with $KMnO_4$ or $PhCO_3H$ see p. 103; *Zelinsky*, Ber. **64**, 1399; *Bedos*, C. r. **196**, 625. For the possibility of a dihydrobenzene containing twin double bonds of the allene type see *Lely*, Chem. Weekbl. **22** (1925), 501.

On oxidation at 0° with 1% $KMnO_4$ solution 1,4-cyclohexadiene gives an *erythritol* which crystallises with 2 aq. and melts at 241–242° when anhydrous. It is possibly the racemic form of the optically active erythritol, m.p. 224°, isolated by *v. Lippmann* from sugar beet juice. On oxidation with perbenzoic acid *cyclohexadiene dioxide*, m.p. 110°, is formed. This, when heated with water, gives the *monohydrate*, m.p. 195°, of the erythritol mentioned above (*Zelinsky*, Ber. **64**, 1399).

$\Delta^{1,3}$-Dihydrotoluene, C_6H_7Me, b.p. 111°, from m-amino-hexahydrotoluene phosphate, gives on oxidation with $KMnO_4$ methyl-dihydroxy-cyclohexanone (methyl-cyclohexanone-diol) (p. 111), and finally succinic and oxalic acids; this establishes its constitution, but it is not homogeneous (*Harries*, Ber. **41**, 1698). **$\Delta^{2,4}$-Dihydrotoluene,** b.p. 106°, d_{20} 0·8274; **$\Delta^{2,6}$-dihydrotoluene,** b.p. 109°, d_{20} 0·8292 (*Zelinsky*, Ber. **41**, 2484, 2630).

For **1,1-dimethyl-cyclohexadiene,** see *Crossley*, J. **95**, 930.

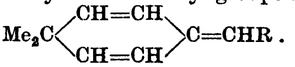
1,2-Dimethyl-$\Delta^{2,6}$-cyclohexadiene, *dihydro-o-xylene, cantharene*, $C_6H_6Me_2$, b.p. 135·5°, is produced when cantharic acid, $C_{10}H_{12}O_4$, a rearrangement product of cantharidin, is distilled with soda lime. Its odour resembles that of turpentine, and it resinifies on exposure to the air (*Piccard*, Ber. **25**, 2453; *Harries*, Ann. **328**, 115). It has been made synthetically from 1-methyl-Δ^1-cyclohexene by way of 1-methyl-Δ^6-cyclohexene-2-one and 1,2-dimethyl-Δ^6-cyclohexene-2-ol (*cantharenol*) (*Haworth*, J. **103**, 1242).

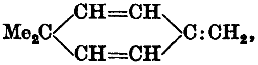
$\Delta^{3,5}$-Dihydro-m-xylene, b.p. 129°, d_{18} 0·8203, is obtained from 3,5-diamino-1,3-Me_2-cyclohexane, and by reduction of 1,3-Me_2-5-chloro-cyclohexadiene-3,5, the product of the action of PCl_5 upon 1,3-Me_2-cyclohexenone (*Auwers*, Ber. **43**, 3111). For **$\Delta^{2,4}$-dihydro-m-xylene,** b.p. 129°, d_{20} 0·8225, see *Zelinsky*, Ber. **41**, 2631. A mixture of hydrocarbons containing a dihydro-m-xylene, together with m-xylene and tetrahydro-m-xylene, has been obtained from methyl-heptenone $Me_2C{:}CH{\cdot}CH{\cdot}CH_2COMe$ (p. 203) by condensation with $ZnCl_2$ (*Crossley*, J. **95**, 935).

$\Delta^{1,3}$-1,3-Diethylcyclohexadiene, b.p. 68°/9 mm. (*Blaise, Maire*, Bull. **3** (1908), 420).

$\Delta^{1,3}$-Dihydro-p-xylene, b.p. 135°–138°, d_{19} 0·8314, has been obtained by a curious reaction which consists in boiling dichloro-α,β-pulenone (p. 120) with alcoholic potash; it polymerises easily. Oxidation with $KMnO_4$ gives acetyl-acetone, which proves its constitution (*Auwers*, Ber. **41**, 1816; **42**, 2404). **$\Delta^{2,4}$-Dihydro-p-xylene,** b.p. 133° (*Zelinsky*, Ber. **41**, 2633).

1,1,3-Trimethyl-2-methylene-Δ^3-cyclohexene, $C_{10}H_{16}$, b.p. 48·5–49°/11 mm., is formed, instead of the iodide which would be expected, by the action of KI in acetone on the bromide obtained from β-cyclogeraniol (p. 203) and HBr (*Kuhn*, Ber. **67**, 357).

Semibenzenes is the name given by *Auwers* (Ann. **425**, 217) to hydro-aromatic hydrocarbons with two endocyclic double bonds in $\Delta^{1,4}$-position and one semicyclic double bond, with methyl or other alkyl groups attached to the ring. The general formula is  $Me_2C\langle{}^{CH=CH}_{CH=CH}\rangle C{=}CHR$. These hydrocarbons are isomeric with the true benzenes. They are obtained from the tertiary carbinols of methylated dihydrobenzenes (p. 105) by shaking with ice-cold 10% sulphuric acid. They are very unstable and show a great tendency to polymerise. When heated with acids they undergo a rearrangement to the corresponding benzene hydrocarbons; heat alone does not bring about this change.

1,1-Dimethyl-4-methylene-$\Delta^{2,5}$-cyclohexadiene,  $Me_2C\langle{}^{CH=CH}_{CH=CH}\rangle C{:}CH_2$, b.p. 37–39°/15 mm.; **1,1-dimethyl-4-ethylidene-$\Delta^{2,5}$-cyclohexadiene,** b.p. 71–72°/15 mm. For other homologous semibenzenes see *Auwers*, l. c.

Cyclohexyl-acetylenes. — For steric reasons derivatives of cyclohexane with a triple bond in the ring could hardly be expected to exist, or would be extremely unstable; the same holds true for compounds with two double bonds in the ring in the allene position. Cyclohexyl-acetylenes with a triple bond in the side chain can, however, be obtained by the methods used in the aliphatic series.

Cyclohexyl-acetylene, $C_6H_{11}\cdot C{\vdots}CH$, b.p. 131–132° is obtained from cyclohexyl-chloro-ethylene with KOH, or from cyclohexyl-ethylene dibromide or from hexahydro-acetophenone (p. 124) through the dichloride; it gives a Na-salt, which with CO_2 forms cyclohexyl-propiolic acid (p. 134) (*Jegorova,* C. 1912 I 1010). **Cyclohexyl-allylene,** *hexahydrobenzyl-acetylene,* $C_6H_{11}CH_2C{\vdots}CH$, b.p. 55–58°/15 mm. (*Lecomte,* C. r. **183**, 27). For higher homologues see *Bourguel,* Ann. chim. **3** (1925), 385.

2. RING ALCOHOLS OF THE HYDROAROMATIC HYDROCARBONS

(a) Ring Alcohols of the Cyclohexane Group. — The cyclic alcohols of this group occurring in nature include compounds such as quercitol and inositol, which were formerly classed with the sugars, and the saturated monocyclic terpene alcohols described among the terpenes (p. 216). In the laboratory the hydroaromatic ring alcohols have been prepared by catalytic reduction of phenols, cyclohexenols, polyhydroxy-benzenes etc. with H_2 and finely divided metals, such as Ni and Pd, and also from other hydroaromatic compounds, chiefly from the corresponding ketones. These latter yield, by reduction, *secondary* cyclic alcohols, and, by interaction with Mg-alkyl iodides (I 218) *tertiary* cyclic alcohols (*Zelinsky,* Ber. **34**, 2877; *Sabatier, Senderens,* Ann. ch. phys. (8) **10**, 527). In some cases it has been possible to isolate a cyclohexanone, the tautomeric form of the tetrahydrophenol, as an intermediate in the catalytic hydrogenation of phenols (*Vavon,* C. r. **172**, 1231). Cyclohexanols have also been obtained by the action of oxygen upon cyclohexyl-Mg halides, from the cyclic amines with HNO_2, and by the addition of the elements of water to cyclohexenes on heating with glacial acetic acid and concentrated H_2SO_4. Most alkyl-cyclohexanols occur in stereoisomeric forms.

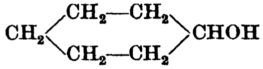
For the geometrical and optical isomerism of methylcyclanols see *Gough, Hunter, Kenyon,* J. **1926**, 2052. For the separation of isomers by azeotropic methods see *Lacourt,* Belg. **36** (1927), 346. For their separation by means of the p-nitrobenzoates or of the hydrogen phthalates see *Gough* et al. l. c. The cis forms of the alcohols differ from the trans isomers in their greater specific viscosity, but the differences in other physical properties are less marked (*Auwers,* J. pr. **124**, 209). Most cis forms undergo dehydration more easily than the trans forms (*Vavon,* Bull. **49** (1931), 567).

The dehydration of hydroaromatic alcohols may be accompanied by changes in the ring (*Meerwein,* Ann. **417**, 255).

General reactions of cyclohexanols: On loss of water (by oxalic acid, dilute H_2SO_4 or catalytically), cyclohexanols are converted into cyclohexenes. They are changed into chloro-cyclohexanes by the action of hydrogen chloride or PCl_5 (*Juéry,* Bull. **17** (1915), 167). They give esters with aliphatic or aromatic carboxylic acids (*Senderens,* C. r. **155**, 1012, 1254). On oxidation adipic acid and its homologues are obtained. When treated with alkalies, they are converted into cyclohexyl-cyclohexanols (*Guerbet,* C. r. **164**, 952). They also condense with aliphatic alcohols to cyclohexyl alcohols. Addition compounds with phenols, formed in aqueous alkaline solution, have been described in Germ. Pat. 484,994.

Cyclohexanol	m.p. 23·5°	b.p. 161·5°
cis-1,2-**Methylcyclohexanol**		b.p. 165·2/165·4°/761mm.
trans-1,2-**Methylcyclohexanol**		b.p. 167·2-167·6°/760 mm.
cis-1,3-**Methylcyclohexanol**	m.p. 38°	b.p. 175·5°/760 mm.
trans-1,3-**Methylcyclohexanol**		b.p. 174·5-174·7°/762 mm.
cis-1,4-**Methylcyclohexanol**		b.p. 175·5°/760 mm.
trans-1,4-**Methylcyclohexanol**		b.p. 174·5°/760 mm.
1,1-Dimethylcyclohexanol-2		b.p. 77—78°/12 mm.
1,1-Dimethylcyclohexanol-3	m.p. 12°	b.p. 73–74°/8 mm.
1,1-Dimethylcyclohexanol-4		b.p. 76·5°/9·5 mm.
1,2-Dimethylcyclohexanol-1		b.p. 166°
1,3-Dimethylcyclohexanol-3		b.p. 79–81°/21 mm.
1,4-Dimethylcyclohexanol-4		b.p. 70—72°/12 mm.
cis-**1,3-Dimethylcyclohexanol-5**	m.p. 38°	b.p. 89°/16 mm.
$2^{c},4^{tr}$-Dimethylcyclohexanol-1^{c}		b.p. 176–176·5°
$2^{tr},4^{c}$-Dimethylcyclohexanol-1^{c}		b.p. 175–176°
$2^{c},5^{tr}$-Dimethylcyclohexanol-1^{c}		b.p. 180°
$2^{c},6^{tr}$-Dimethylcyclohexanol-1^{c}		b.p. 172°
1-Ethylcyclohexanol	m.p. 33°	b.p. 166°
4-Ethylcyclohexanol-1		b.p. 162–165°
1,1,2,-Trimethylcyclohexanol-2		b.p. 75·8°/16 mm.
1,1,3-Trimethylcyclohexanol-3	m.p. 74°	
1,1,4-Trimethylcyclohexanol-4	m.p. 58°	b.p. 75°/11 mm.
1,3,5-Trimethylcyclohexanol-5		b.p. 82–83°/19 mm.
cis-**2-Propylcyclohexanol**		b.p. 84°/10 mm.
trans-**2-Propylcyclohexanol**		b.p. 90°/14 mm.
3-Isopropylcyclohexanol		b.p. 114°/28 mm.
1,1,4,4-Tetramethylcyclohexanol-2	m.p. 53°	b.p. 201·5–203°/745 mm.

Cyclohexanol, *hexahydrophenol, "hexalin", "adronol"*



is formed (1) from cyclohexanone by reduction with sodium and moist ether (*Auwers*, C. 1927 II 1564); (2) from 4-iodo-cyclohexanol, the product of the reaction of HI upon quinitol, by reduction with zinc dust and glacial acid; (3) from amino-cyclohexane (see below) with nitrous acid (*Markovnikov*, Ann. **302**, 20); (4) by passing gaseous phenol and hydrogen over finely divided Ni at about 170° (Germ. Pats. 383,540, 408,811, 444,685); (5) by the action of oxygen upon cyclohexyl-magnesium chloride (*Sabatier*, Ann. chim. phys. (8) **10**, 527; *Wuyts*, Belg. **36**, 222); (6) from Δ^2-cyclohexenol by reduction with H_2 in the presence of Pd + $BaSO_4$ (*Criegee*, Ann. **481**, 285). It smells like fusel oil, and is more soluble in water than the aliphatic alcohols with six carbon atoms (*Baeyer*, Ber. **26**, 229). When water is removed by means of H_2SO_4, $KHSO_4$ etc., cyclohexene is formed (*Senderens*, C. r. **154**, 1168; *Lacourt*, Belg. **36**, 346). *Phenylurethane* m.p. 81·5°. *Acetyl compound* m.p. 104°. With HBr it forms bromocyclohexane (p. 91). Its oxidation with nitric acid (density 1·2) or with $KMnO_4$, is a method of preparing adipic acid, which is obtained in excellent yield (*Mannich*, Ber. **41**, 575; *Bouveault*, Bull. **3** (1908), 432; *v. Braun*, Ber. **55**, 3526).

For *esters* of cyclohexanol see *Senderens*, C. r. **155**, 1012, 1254.

Cyclohexyl-alkyl and *-alphyl ethers* are obtained from cyclohexanol and the corresponding halides with $NaNH_2$. **Cyclohexyl-methyl ether,** *hexahydroanisole*, $C_6H_{11}OMe$, b.p. 134·5–135°, is obtained from sodium-cyclohexanol and MeI, by reducing anisole with H_2 and Ni (*Waser*, Helv. **12**, 418), and by reducing 1-methoxy-Δ^4-cyclohexene (p. 105) catalytically (*Wieland*, Ber. **59**, 2490). When the methyl ethers of phenols are hydrogenated under pressure, the methyl group attached to oxygen is often split off as CH_4 or MeOH (*Waser*, Helv. **12**, 421). For *methoxy derivatives* of cyclohexanol of the general formula $C_6H_{11}\cdot OCH_2\cdot OR$ see *Palfray*, Bull. **43** (1928), 900.

Cyclohexyl-chloromethyl ether, $C_6H_{11}\cdot OCH_2Cl$, b.p. 75°/14 mm., is prepared from cyclohexanol, formaldehyde and HCl. In this compound Cl can be substituted by OAlkyl or OAcyl, and it reacts with *Grignard* compounds.

Cyclohexyl-allyl ether, from sodium-cyclohexanol and C_3H_5Br, b.p. 169–172°, does not undergo the *Claisen-Eisleb* rearrangement (vol. III) into allyl-cyclohexanol (*Claisen*, Ann. **418**, 73).

Dicyclohexyl ether, $C_6H_{11}\cdot O\cdot C_6H_{11}$, b.p. 116°/15 mm., is obtained from diphenylether with H_2 and Ni (*Ipatiev*, Ber. **41**, 1001), or from cyclohexanol with p-toluene-sulphonic acid in an autoclave at 170° (*Lacourt*, Belg. **36**, 346).

Cyclohexyl-phenyl ether, b.p. 125–127°/10 mm., is obtained from iodobenzene + potassium cyclohexanol, or, together with **p-cyclohexyl-phenol,** m.p. 131–133°, from cyclohexanol + phenol. It undergoes a rearrangement, when heated, into o- and p-cyclohexyl-phenols; this reaction is analogous to the *Claisen-Eisleb* transformation of allyl-phenyl ethers. As the same products are obtained from cyclohexene + phenol, it seems that cyclohexyl-phenyl ether first decomposes into these two substances which then re-unite (*Schrauth*, Ber. **57**, 856; *Skraup*, ib. **60**, 1074; Brit. Pat. 294,238). **Cyclohexyl-benzyl ether,** b.p. 165·5–166·5°/37 mm. (*Senderens*, C. r. **183**, 830; *Cornubert*, Bull. **43** (1928), 74).

2-Chloro-cyclohexanol, cis form, b.p. 93—94°/26 mm., has been obtained by reduction of 2-chloro-cyclohexenol with tert. butyl-magnesium chloride; and the trans form, b.p. 93°/26 mm., from cyclohexene and HOCl, or from cyclohexene oxide and HCl (*Godchot*, C. r. **176**, 448; *Bartlett*, Am. **57**, 224). **2-Bromo-cyclohexanol,** m.p. 27·5°; **2-amino-cyclohexanol** m.p. 65·6° (*Swartz*, Acad. Belg. **22** (1936), 105, 924).

1-Methylcyclohexanol is produced by ring synthesis in the action of Mg-1,5-dibromo-pentane upon ethyl acetate (p. 18) (*Grignard*, C. r. **144**, 1358). **2-Methylcyclohexanol,** cis, m.p. — 9·3°, b.p. 165°, d_{16} 0·9381, $n_{D_{18}}$ 1·46539, from o-cresol by hydrogenation in presence of colloidal Pt. *Hydrogen phthalate* m.p. 104°; *p-nitrobenzoate* m.p. 53°. Trans form m.p. — 21°, b.p. 167°, d_{19} 0·9245, $n_{D_{19}}$ 1·46200, from commercial 2-methyl-cyclohexanol by means of the *hydrogen phthalate* m.p. 124°; *p-nitrobenzoate* m.p. 65° (*W. Hückel*, Ber. **64**, 2892). **3-Methylcyclohexanol** has been obtained in its laevorotatory form, $[\alpha]_D$ — 3°40′, by reduction of optically active 3-methyl-cyclohexanone (*Zelinsky*, Ber. **30**, 1534). **4-Methylcyclohexanol** forms two isomeric neutral esters with oxalic acid, one a solid m.p. 98°, the other a liquid, b.p. 196–199°/16 mm. The alcohols regenerated from the esters are identical and give a *phenylurethane* melting at 126° (*Juéry*, Bull. **17** (1915), 167). For other physical constants of the three methylcyclanols see *Eisenlohr*, C. 1926 I 75. Cis and trans chlorohydrins of Δ^1-methylcyclohexene: *Bartlett*, Am. **56**, 1990. β-Glucosides of the isomeric methylcyclanols are produced when the alcohols, dissolved in dry ether, are shaken with β-aceto-bromo-glucose and $AgNO_3$. The acetyl compounds so formed are then hydrolysed (*Hamalàinen*, C. 1914 I 1887).

Dimethyl-cyclohexanols. — *v. Braun* (Ber. **60**, 2438) has prepared all the cyclanols which are theoretically obtainable by reducing 1,3,5-xylenol. **4-Ethyl-cyclohexanol** is obtained by catalytic reduction of p-dihydroxy-diphenylmethyl-methane (Brit. Pats. 254,753, 274,439). **3,6,6-Trimethyl-cyclohexanol,** *pulenol*, b.p. 188° (see p. 120).

2-Propylcyclohexanol is obtained, together with 25–30$^0/_0$ of propyl-cyclohexane, from allyl-phenol by hydrogenation with Pt in glacial acetic acid. Propylcyclohexanone is an intermediate. *Phenylurethane* m.p. 97–97·5°. The cis form, b.p. 84°/10 mm., has been isolated by means of the phthalate. The trans form is obtained (1) with Na and EtOH from o-propyl-cyclohexanone (prepared from the mixture of both alcohols with chromic acid mixture), or preferably (2) from the Na-compound of the cis form at 190–200°. B.p. 90°/14 mm., *phenylurethane* m.p. 69–70° (*Vavon*, Bull. **41**

(1927), 1638). **3-Isopropylcyclohexanol,** from isopropyl-dihydroresorcinol through 5-chloro-3-isopropyl-Δ^4-cyclohexene-3-one, is of interest in the synthesis of terpene derivatives (*Crossley,* J. **107,** 171).

Hexahydrothymol and hexahydrocarvacrol see Menthol and Carvomenthol, pp. 216 and 218.

3-Methyl-6-propyl-, 3-methyl-6-isobutyl-, and **3-methyl-6-isoamyl-cyclohexanol,** b.p. 112°/22 mm., m.p. 69°, and b.p. 137°/23 mm. respectively, are obtained synthetically by heating 3-methylcyclohexanone with sodium and propyl, isobutyl or isoamyl alcohol to about 220° (*Haller,* C. r. **140,** 474, 624).

Acetylene-substituted cyclohexanols of the type $C_5H_{10}{>}C(OH){\cdot}C{\vdots}CH$ (*ethinyl-cyclohexanols*) are prepared from cyclohexanones and C_2H_2 by means of $NaNH_2$. When treated with strong formic acid they undergo a remarkable change into unsaturated aldehydes of the type $C_6H_{10}{:}CH{\cdot}CHO$ (p. 122), which are characterised by a strong smell (*Rupe,* Helv. **9,** 672); by partial reduction, they are converted into vinyl-cyclanols. For the action of $SOCl_2$ upon ethinyl-cyclohexanol see *Hund,* Am. **56,** 1924.

Polyhydric cyclic alcohols are produced (1) by reduction of polyketo-cyclohexanes; (2) from polyhydric phenols by reduction with hydrogen and nickel (*Sabatier,* C. r. **146,** 1193); (3) from cyclohexenes by mild oxidation with $KMnO_4$, or from the corresponding halogen hydrins; (4) from chloro-cyclohexanols through the acetates (*Senderens,* C. r. **173,** 1365; *Palfray,* ib. **186,** 872; *Derx,* Rec. **41,** 312); (5) from the oxides by addition of the elements of water (*Nametkin,* C. 1925 I 222).

The three dihydroxy-cyclohexanes react with dilute sulphuric acid differently and with varying readiness. The 1,2-isomer gives mainly condensed hydrocarbons and a little 1,3-cyclohexadiene; the 1,3-diol reacts readily, giving much 1,3- and little 1,4-cyclohexadiene; on the other hand, the 1,4-isomer gives only little 1,3- and much 1,4-cyclohexadiene (*Senderens,* C. r. **177,** 1183). The cyclane-diols and-triols, like the cyclanols, often occur in stereo-isomeric forms. These can be separated by means of their different reactivity with acetone (*Lindemann,* Ann. **483,** 34). A change of configuration often takes place when the cyclane-diol acetates are treated with hydrogen halides, but not when the dichloro-cyclanes react with silver acetate (*Palfray,* C. r. **186,** 872; **190,** 942; Bull. **45** (1929), 855). For references to cyclane-diols see *Rothstein,* Ann. chim. **14** (1931), 461. Alkyl ethers of cyclane-diols: *Helfer,* Helv. **7,** 950; *Sabetay,* Bull. **47** (1930), 214.

trans-**Cyclohexane-1,2-diol,** *o-dihydroxy-hexahydrobenzene,* $C_6H_{10}[1,2](OH)_2$ m.p. 100°, b.p. 225°, is obtained from cyclohexene with $KMnO_4$ (*Markovnikov,* Ann. **302,** 21; *Nametkin,* C. 1925 I 222; *Senderens,* C. r. **180,** 790), and by reduction of pyrocatechol. The isomeric cis **1,2-cyclohexane-diol,** m.p. 105°, b.p. 236° (*Lindemann,* Ann. **483,** 31), is produced from the iodo-hydrin, *2-iodo-cyclohexanol,* $C_6H_{10}I(OH)$, m.p. 42°, obtained from cyclohexene with iodine and mercuric oxide. This yields with silver oxide and KOH, first *cyclohexene oxide,* $C_6H_{10}O$, b.p. 131°, which resembles ethylene oxide and combines with water to form cis 1,2-cyclohexane-diol, with bisulphite to *cyclohexanol-sulphonic acid,* $C_6H_{10}(OH)SO_3H$, and with ammonia to *amino-cyclohexanol* $C_6H_{10}[1,2](NH_2)(OH)$, m.p. 66°, b.p. 219° (*Brunel,* Ann. chim. phys. **6** (1905), 200).

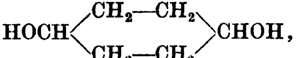
The cis diol has also been obtained from the oxide by way of the *toluene-sulphonic mono-ester* of the trans diol, m.p. 96° and its *acetate* m.p. 78°, a reaction involving a double Walden rearrangement (*Criegee,* Ber. **69,** 2753).

Hexahydroguaiacol, b.p. 175–180°/730 mm. (*Waser,* Helv. **12,** 418).

1-Methyl-cyclohexane-1,2-diol, cis m.p. 67·5–68·5° (*Verkade,* Ann. **467,** 217), and trans m.p. 84–84·5°, is obtained from Δ^1-methyl-cyclohexene, and from 1-methyl-cyclohexene-1-one-6 (*Dupont,* Belg. **45,** 57, 113). When heated with oxalic acid it yields 2-methyl-cyclohexanone-1. For the products obtained from cis and trans-methyl-cyclohexane-diols by removal of water see *Tiffeneau,* C. r. **202,** 1931.

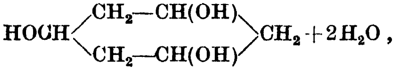
1,2-Dimethyl-1,2-cyclohexane-diol is transformed into *1-methyl-1-acetyl-cyclopentane* (p. 60) by treatment with dilute H_2SO_4, or with water at 180°; when the secondary alcohol corresponding to this ketone is dehydrated, the 6-ring is reformed, 1,2-dimethyl-Δ^1-cyclohexene being obtained (*Meerwein*, Ann. **417**, 264). **1,4-Dimethyl-3,4-cyclohexane-diol** cis, m.p. 88–89°, is obtained from the oxide with water, and trans, m.p. 77°, from the corresponding cyclohexene with $KMnO_4$. Similarly: **1-Methyl-4-ethyl-3,4-cyclohexane-diol,** cis m.p. 82° and trans m.p. 76–77° (*Wallach*, Ann. **396**, 267; *Nametkin*, C. 1925 I 222).

1,3-Cyclohexane-diol, *resorcitol*, cis m.p. 84·5°, trans m.p. 115·5° is prepared by reduction of resorcinol with H_2 and Ni at 130° (*Sabatier*, C. r. **146**, 1193). Two stereoisomeric dibromo-cyclohexanes, m.ps. 112 and 1°, are formed from the two diols with HBr (*Palfray*, C. r. **190**, 189; *Skita*, Mo. **53/54**, 753; *Lindemann*, Ann. **477**, 78). **2-Chloro-resorcitol** m.ps. 90° and 135°, is obtained from Δ^2-cyclohexenol with HOCl (*Kotz*, J. pr. **111**, 373).

Cyclohexane-1,4-diol, *quinitol*,  $HOCH\left\langle\begin{matrix}CH_2-CH_2\\CH_2-CH_2\end{matrix}\right\rangle CHOH$, cis m.p. 102°, trans m.p. 139° is formed by reducing cyclohexane-1,4-dione (p. 112) with sodium amalgam in the presence of carbon dioxide (*Baeyer* 1892), and also by reducing hydroquinone with H_2 and Ni. It tastes sweet at first and then bitter, and is readily soluble in water and in alcohol. Chromic acid oxidises it to quinone (*Baeyer*, Ber. **25**, 1038). When heated with 60% H_2SO_4 it condenses in part to a hydrocarbon, which is probably phenyl-cyclohexane (p. 91) (*Willstatter*, Ber. **34**, 506). Quinitol serves as starting material for the preparation of the simple hydrogenated derivatives of benzene (*Baeyer*, Ber. **26**, 229). Hydriodic acid converts it into 4-iodo-cyclohexanol and 1,4-di-iodo-cyclohexane. By reduction the first yields cyclohexanol, the second cyclohexane (p. 90). When heated with $KHSO_4 + MgSO_4$, quinitol gives Δ^3-cyclohexenol (p. 105), or, by more vigorous action, $\Delta^{1,3}$- and $\Delta^{1,4}$-cyclohexadiene (*Zelinsky*, Ber. **64**, 1399). Reactions of quinitols and their esters with hydrogen halides are described by *Palfray* and *Rothstein* (C. r. **190**, 942). 1,4-Dibromo-cyclohexane passes readily into dihydrobenzene (p. 96). **2,5-Dimethyl-quinitol** is obtained from the corresponding diketone (*Baeyer*, Ber. **25**, 2122; **26**, 230).

Cyclohexane-1,2,3-triol, *pyrogallitol*, three forms: α, m.p. 108°, β, 124–125°, γ, 148° has been prepared from Δ^2-ethoxy-cyclohexene with $KMnO_4$: the ethoxy-cyclohexane-diol obtained is hydrolysed by conc. HBr (*Brunel*, C. r. **150**, 986). It is also obtained by hydrogenation of pyrogallol under pressure (*Lindemann*, Ann. **483**, 37).

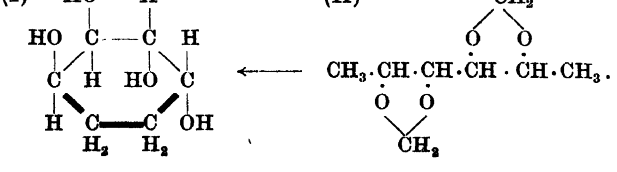
Cyclohexane-1,3,5-triol, *phloroglucitol*,

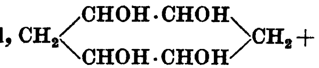


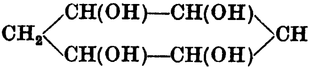
$$HOCH\left\langle\begin{matrix}CH_2-CH(OH)\\CH_2-CH(OH)\end{matrix}\right\rangle CH_2 + 2H_2O\,,$$

α-form, hydrated, m.p. about 110°, anhydrous, m.p. 184°, β-form, anhydrous, m.p. 145°. Hydrogenation of phloroglucinol gives both α- and β-forms (*Lindemann*, Ann. **477**, 78). **Cyclohexane-1,2,4-triol,** *hydroxy-quinitol*, m.p. 122°: *Zelinsky*, Ber. **64**, 1403.

Cyclohexane-1,2,3,4-tetrol, (I), m.p. 229°. Its *di-methylene ether*, m.p. 148°, is obtained from 1,6-desoxy-dimethylene-mannitol, (II) (*Micheel*, Ann. **496**, 96). The latter is first converted into a di-iodide CH_2I . . . CH_2I, the ring is closed by the action of molecular Ag, and finally the methylene groups are removed by hot dilute HCl:



Cyclohexane-1,2,4,5-tetrol,  $CH_2\begin{matrix}\diagup CHOH\cdot CHOH \diagdown \\ \diagdown CHOH\cdot CHOH \diagup\end{matrix}CH_2 + 2H_2O$, m.p. anh. 241–242°, is prepared from $\Delta^{1,4}$-cyclohexadiene (p. 96) with $KMnO_4$. This compound gives with perbenzoic acid **cyclohexadiene-1,2,4,5-dioxide,** $O{:}C_6H_8{:}O$, m.p. 110° (*Zelinsky,* Ber. **64,** 1399).

Cyclohexane-pentol, *quercitol,*  $CH_2\begin{matrix}\diagup CH(OH)—CH(OH) \diagdown \\ \diagdown CH(OH)—CH(OH) \diagup\end{matrix}CH(OH)$, m.p. 235°, $[\alpha]_D = +24{\cdot}16°$, occurs in acorns; the aqueous extract of these can be freed from glucose by fermentation with yeast, which does not attack quercitol. It is also found in considerable quantity (1·35%) in the leaves of the palm *Chamaerops humilis* (*Müller,* J. **91,** 1766). Its configuration is the same as that of active inositol (see below) (*Karrer,* Helv. **9,** 116). Quercitol is converted by hydriodic acid into a mixture of benzene, hexane, phenol, quinone and hydroquinone (*Prunier,* Ann. chim. (5) **15,** 70). It is oxidised by nitric acid to mucic acid and trihydroxy-glutaric acid; with $KMnO_4$ it gives mainly malonic acid, together with oxalic acid and CO_2 (*Kiliani,* Ber. **29,** 1762). A laevorotatory quercitol, m.p. 174° anhydrous, $[\alpha]_D = -73{\cdot}9°$, has been found in the leaves of *Gymnema sylvestre; penta-acetyl derivative* m.p. 125° (*Power, Tutin,* J. **85,** 624). — For the configuration of quercitol see *Posternak,* Helv. **15,** 948.

Inositol, *cyclohexane-hexol,* $C_6H_6(OH)_6$, can occur theoretically in seven inactive forms, two optically active forms and one racemic form, which differ in the relative positions of the hydroxyl groups. Both optically active forms, $[\alpha]_D$ molten ± 65°, are known with certainty, and also the racemic form, together with several inactive forms which have not yet been investigated in detail. The configuration of inositol will be found in vol. I, p. 43. For the photosynthesis of inositol from $CO_2 + H_2O$ see *Kogl,* Bioch. Z. **95,** 313; **97,** 21; the first product seems to be tetrahydroxy-ethylene, three molecules of which polymerise to dodecahydroxy-cyclohexane $C_6(OH)_{12}$; this is then reduced to inositol. By removal of oxygen cyclohexanone is thought to be formed, and the latter yields hexylene aldehyde and caproic acid (I, 255, 306) when exposed to light (*Ciamician,* Ber. **41,** 1071). — For the preparation of inositol by catalytic reduction of hexahydroxy-benzene with Pd-black in aqueous solution at 55°, see *Wieland,* Ber. **47,** 2082.

The hexaphosphate of inositol, $C_6H_{18}O_{24}P_6$, has been identified by *Posternak* (C. r. **169,** 138) with "*phytin*", the organic phosphorus reserve material of green plants. It has been prepared artificially by *Wallach,* (Ann. **389,** 169). Inositol-polyphosphoric acids have also been found in cotton seed (*Rather,* Am. **39,** 777). *Anderson* (Am. **52,** 1607; C. 1930 II 3793) has detected phosphatides and lipoids of inositol in human tubercle bacilli, and *Momose* (Biochem. J. **10,** 120) has found a lipoid in the brain. The Ca-Na salt of the hexaphosphate, $C_6H_{12}O_{27}P_6\cdot Ca_2Na_8$, and other inositol-phosphoric salts have been prepared by *Otolski,* C. 1932 II 3741.

i-Inositol, *phaseomannitol, dambose,* $C_6H_6(OH)_6 + H_2O$, m.p. 225–226° (anhydrous), occurs in the muscles of the heart and in the urine when there has been an excessive consumption of water, also in unripe beans from *Phaseolus vulgaris,* in citrus fruit and in unripe peas. If heated to 170° with hydriodic acid it yields phenol, di-iodo-phenol, and traces of benzene (*Maquenne*). Concentrated nitric acid oxidises it to di- and tetrahydroxy-quinones (vol. III), and to rhodizonic and leuconic acids (*Kobert,* Chem.-Ztg. **1887,** 676; *Tanret,* C. r. **109,** 908; *Müller,* J. **91,** 1780; *Contardi,* Chim. applic. **14** (1924), 288). It yields furfural on heating with P_2O_5 (*Neuberg,* Bioch. Z. **9,** 551). **Dambonitol,** $C_6H_6(OH)_4(OMe)_2 + 3H_2O$, is the dimethyl ether of i-inositol. It occurs in the rubber from the Gabon district of the French Congo. By treating the *hexa-acetate* of i-inositol (m.p. 211°) with glacial acetic + HI *Müller* (J. **101,** 2383) obtained two new isomers:

Iso-inositol, m.p. 246–250°, and **pseudo-inositol,** which is hygroscopic. The *hexa-acetate* of the first melts at 112°, and that of the second is amorphous.

d-Inositol, m.p. 247°, [α]D + 65°, from pinitol by the action of HI, behaves with nitric acid like i-inositol. **Pinitol,** *matezitol,* $C_6H_6(OH)_5(OMe)$, m.p. 186°, [α]D + 65·51°, is present in the juice of the root of *Pinus lambertiana,* in the rubber from *Mateza roritina,* a liana from Madagascar, and in the wood of *Sequoia gigantea* (*Sherrard,* Ind. Eng. Chem. **20,** 722).

l-Inositol, m.p. 238°, [α]D –55°, from quebrachitol by means of HI, gives the same products with nitric acid as the two other forms. **Quebrachitol,** $C_6H_6(OH)_5OMe$, m.p. 191°, [α]D –80°, occurs in quebracho bark, in the latex of *Hevea brasiliensis* (*Morani,* C. 1925 I 533) and in *Heterodendron oleaefolium* (*Patterson,* C. 1931 II 553). Esters of quebrachitol are mentioned by *Levi,* Gazz. **59,** 550. **d,l-Inositol,** m.p. 253°.

Scyllitol, *cocositol, quercinitol,* $C_6H_{12}O_6$, m.p. 348·5°, which is probably an inactive inositol, was discovered by *Stadeler* in 1856. It is found in the organs of various plagiostomes (the family of fishes which includes the sharks and rays, e.g. *Scyllium canicula*) and very plentifully in the kidneys of roach and shark, from which it is separated by means of its sparingly soluble lead salt (*Muller,* Ber. **40,** 1821), also in the eggs of the dog-shark (*Micheel,* Ann. **496,** 78) and in the leaves of *Cocos nucifera* and *Cocos plumosa.* It is very similar to inositol in its behaviour, and like the latter is oxidised to rhodizonic acid by H_2O_2. The *hexa-acetyl* compound melts at 290–291° (*Müller,* J. **101,** 2383).

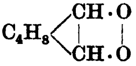
Mytilitol, *methyl-inositol,* $C_6H_5Me(OH)_6$, $2\,H_2O$, m.p. 259°, occurs in the mussel *Mytilus edulis* (*Ackermann,* Ber. **54,** 1938). *Penta-acetate* m.p. 157–158°, *hexa-acetate* m.p. 182°.

There are theoretically possible 25 isomeric forms of cyclohexane-tetrol, 16 isomeric forms of cyclohexane-pentol and 9 isomeric forms of cyclohexane-hexol. Of these fifty compounds only seven have been found in nature. *Patterson* (Nature **126,** 880) has suggested that the natural cyclic alcohols all have their origin in glucose or a compound of similar stereochemical configuration, from which only fourteen of the fifty compounds can be derived.

Phenose, $C_6H_6(OH)_6$ (?), is the name given to an amorphous substance obtained by the action of Na_2CO_3 on the addition product of benzene with 3 HOCl, $C_6H_6Cl_3(OH)_3$. It deliquesces in air, has a sweet taste and reduces Fehling's solution; it cannot be fermented (*Carius,* Ann. **136,** 322).

Oxides of the Cyclohexane Series, $C_nH_{2n-2}:O$, have been prepared by *Godchot* and *Bedos* by treating cyclohexenes with I_2 and HgO or with perbenzoic acid (C. r. **175,** 1411). They give 1,2-cyclohexane-diols with boiling water and trans-alkyl-cyclohexanols with alkyl-Mg halides. Their reactions with H_2, HlgH, ethyl malonate and aceto-acetate have been studied by *Kotz,* J. pr. **110,** 104.

Cyclohexene oxide, b.p. 130–132°, see p. 101. **1-Methyl-1,2-cyclohexene oxide,** b.p. 137–138°, and **4-methyl-1,2-cyclohexene oxide,** b.p. 141–142°, are described by *Nametkin,* Ber. **56,** 1803. The latter compound has been obtained by *Markovnikov* (Ann. **336,** 316) from the chlorohydrin of Δ^3-methyl-cyclohexene by treatment with KOH. **1,4-Dimethyl-1,2-cyclohexene oxide,** b.p. 152·5–153°, see *Nametkin,* C. 1925 I 222.

Cyclohexene peroxide,  $C_4H_8\left<\begin{matrix}CH\cdot O\\ | \quad\; |\\ CH\cdot O\end{matrix}\right.$, b.p. 48–50°/1 mm., is formed when cyclohexene and oxygen are exposed to light in the presence of eosin. It gives with sulphuric acid cis cyclohexane-diol and a cyclopentene aldehyde (p. 54) (*Hock, Schrader,* Naturw. **24,** 159).

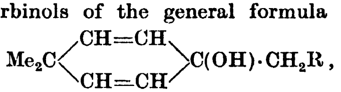
(b) Ring Alcohols of the Cyclohexene Group are obtained: (1) by oxidising cyclohexenes with Os oxides as catalysts (*Medvedev,* C. 1927 II 1012); (2) by dehydrating cyclane diols, using a small quantity of Br_2 as a catalyst (*Sabetay,* Bull. **47** (1930), 463); (3) from dihalogenated cyclohexanes or halogenated cyclohexenes by way of the acetates (*Hofmann*, C. 1926 I 2343); (4) from halogenated cyclohexanols with Na (*Sabetay*, Bull. **48** (1928), 904). Numerous members of this group are dealt with in the section on Terpenes.

Δ^1-Cyclohexenol is tautomeric with cyclohexanone (*Wieland*, Ber. **59**, 2490). Its *methyl ether* (ib. p. 2492), b.p. 36°/12 mm., results from cyclohexanone dimethyl-acetal by removing MeOH, and its acetate (*Mannich*, Ber. **41**, 564) from cyclohexanone by heating with acetic anhydride and sodium acetate. **Δ^2-Cyclohexenol,** b.p. 161–163°, *phenylurethane* m.p. 108°, *naphthylurethane* m.p. 156°, is obtained from cyclohexene with O_2 or with lead tetracetate (*Kötz*, J. pr. **111**, 383; *Criegee*, Ann. **481**, 265). **Δ^3-Cyclohexenol,** b.p. 165–166°, *phenylurethane*, m.p. 81°, is prepared from 4-iodocyclohexanol with quinoline or with Na, and from quinitol or resorcitol by distilling with a little bromine. *Ethyl ether*, b.p. 59–60°/14 mm. (*v. Braun*, Ber. **55**, 3770; *Sabetay*, Bull. **43** (1928), 904; **47** (1930), 463).

Knoevenagel (Ann. **289**, 131) prepared a number of Δ^2-cyclohexenols by reducing 3-alkyl-Δ^2-cyclohexenones (p. 115), e.g. **3-methyl-Δ^2-cyclohexenol,** b.p. 176°.

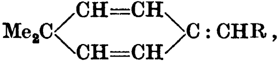
(c) Ring Alcohols of the Cyclohexadiene Group. — Only a few compounds of this class are known. Some ring-unsaturated cyclic ketones (see below) react in the enolic form as dihydrophenols, e.g. *cyclohexene-2-one-1*, prepared by *Kötz* (J. pr. **80**, 489) from cyclohexanol-1-one-2 by removing water with anhydrous oxalic acid.

Some tertiary carbinols of the general formula



$$\mathrm{Me_2C}{<}\begin{matrix}\mathrm{CH{=}CH}\\ \mathrm{CH{=}CH}\end{matrix}{>}\mathrm{C(OH){\cdot}CH_2R},$$

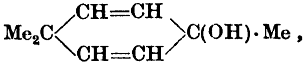
derived from ring-methylated or ring-alkylated $\Delta^{1,4}$-dihydrobenzenes are of interest. They are obtained from the corresponding dichloro-methylated carbinols (p. 118) by reduction with Na and moist ether. They are rather unstable and apt to polymerise. When treated with ice-cold dilute sulphuric acid they lose water and are converted into the so-called semibenzenes



$$\mathrm{Me_2C}{<}\begin{matrix}\mathrm{CH{=}CH}\\ \mathrm{CH{=}CH}\end{matrix}{>}\mathrm{C{:}CHR},$$

(p. 97).

1,1,4-Trimethyl-$\Delta^{2,5}$-cyclohexadiene-4-ol,



$$\mathrm{Me_2C}{<}\begin{matrix}\mathrm{CH{=}CH}\\ \mathrm{CH{=}CH}\end{matrix}{>}\mathrm{C(OH){\cdot}Me},$$

m.p. 43–44°. **1,1-Dimethyl-4-ethyl-$\Delta^{2,5}$-cyclohexadiene-4-ol,** m.p. 46–47°. For other homologues and their chemical behaviour see *Auwers*, Ann. **425**, 222.

1,3-Cyclohexadiene monoxide, b.p. 45°/22 mm., results from *1,3-cyclohexadiene dibromide*, m.p. 108°, by treatment with silver acetate followed by KOH. On hydration it gives a mixture of trans *cyclohexene-3-diol-1,2*, m.p. 77°, and trans *cyclohexene-2-diol-1,4*, m.p. 86° (*Bedos*, C. r. **202**, 671). **Cyclohexadiene-1,2,4,5-dioxide,** $O{:}C_6H_8{:}O$, m.p. 110°, cf. p. 103.

(d) Sulphur Derivatives of the Cyclohexane Alcohols. — **Cyclohexyl mercaptan,** *hexahydro-thiophenol*, $C_6H_{11}SH$, b.p. 158–160°, a colourless, highly refractive oil of penetrating mercaptan odour, is obtained in small quantities by the interaction of halogenated cyclohexanes with KSH, and more easily, by treating ethyl *cyclohexyl xanthate*, $C_6H_{11}S{\cdot}CSOEt$, b.p. 152°/16 mm., with ammonia. It is also prepared by the action of sulphur upon cyclohexyl-magnesium chloride (*Mailhe*, Bull. **7** (1910), 288), or by reduction of *cyclohexane-sulphonyl chloride*, b.p. 127°/15 mm., with tin and HCl. It yields a sparingly soluble mercury salt. **Cyclohexyl-methyl sulphide,** $C_6H_{11}SMe$, b.p. 180°, is obtained from the sodium salt with MeI; **dicyclohexyl disulphide** $(C_6H_{11})_2S_2$, b.p. 288°, from the sodium salt with iodine (*Borsche*, Ber. **39**, 392; **40**, 2220).

(e) Ring Amines of the Cyclohexanes. — These are formed (1) by reduction of nitro-cyclohexanes with zinc or tin and HCl, or of the oximes of the corresponding ketones with sodium in alcoholic solution; 1,3-diamines, in particular, have been obtained by reducing the hydroxylamino-oximes, the addition products of hydroxylamine and cyclohexenone oximes (p. 115); (2) by reduction of anilines with Ni and H_2 (*Sabatier*, C. r. **138**, 457; *Ssadikov*, Ber. **61**, 131); (3) by heating cyclohexanones with ammonium formate or the formates of organic bases (*Wallach*, Ann. **343**, 54) or by treating them at a high temperature with $NH_3 + H_2$ in the presence of a catalyst (Brit. Pat. 265,960); (4) from the cyclohexane carboxylic amides by the action of bromine and alkali (*Gutt*, Ber. **40**, 2061); (5) from cyclohexanol or other primary or secondary cyclic alcohols by heating with primary amines in the presence of Ni (*Guyot*, Bull. **47** (1930), 203; Brit. Pat. 317,079; French Pat. 36,718/673,648); (6) from phenols and aniline by catalytic reduction at 150–185° (Brit. Pat. 314,872; French Pat. 669,824). Tertiary amines are obtained when secondary amines are treated with alkylating agents; the latter are prepared from cyclohexyl halides and primary aliphatic amines (Brit. Pat. 261,747).

Amino-cyclohexane, *cyclohexylamine, hexahydro-aniline,* $C_6H_{11}NH_2$, b.p. 134–135°, is a strong base which smells like coniine; it is only slightly soluble in water. It is prepared from aniline, from cyclohexanone oxime (p. 115), or from *nitro-cyclohexane,* $C_6H_{11}{\cdot}NO_2$, b.p. 206°. If aniline vapour and hydrogen are passed over finely divided nickel at 190°, cyclohexylamine is formed, together with *cyclohexylaniline,* $C_6H_{11}NHPh$, b.p. 171°/30 mm., and *dicyclohexylamine,* $(C_6H_{11})_2NH$, b.p. 145°/30 mm. (*Sabatier*, C. r. **138**, 457; *Skita*, Ber. **52**, 1519). *Acetamino-cyclohexane,* m.p. 104°; the *benzoyl* derivative, m.p. 147°, is also obtained by the *Beckmann* rearrangement of α-hexahydro-benzophenone oxime (p. 130) (*Scharwin*, Ber. **30**, 2863). *Phenyl-urea* derivative, m.p. 180°. *Phenyl-thiourea* derivative, m.p. 147° (*Markovnikov*, Ann. **302**, 22). **Cyclohexyl-methyl-, cyclohexyl-ethyl- and cyclohexyl-dimethyl-amines,** b.ps. 145°, 164° and 165°, are formed by hydrogenating the alkylanilines with H_2 and Ni (*Sabatier*, C. r. **138**, 1257; *Skita*, Ber. **52**, 1527).

Cyclohexyl isothiocyanate, $C_6H_{11}NCS$, b.p. 219°/746 mm., is obtained from cyclohexylamine and CS_2 by two ways: the addition product of the two substances (a dithiocarbamate) is either (preferably) treated with $HgCl_2$ (*Hofmann's* mustard oil synthesis), or is converted into *N,N'-dicyclohexylthiourea,* m.p. 180–181°, which is then distilled with syrupy phosphoric acid (*Skita*, Ber. **53**, 1242; *v. Braun*, ib. 1588).

1,1-Amino-methyl-cyclohexane, $C_6H_{10}(Me)NH_2$, b.p. 143°, is prepared from *1,1-nitro-methyl-cyclohexane,* b.p. 110°/40 mm., and by method (4) (*Nametkin*, C. 1910 II 1377). *Benzoyl* derivative, m.p. 101°.

Hexahydro-toluidines (see *Skita*, Ber. **52**, 1526): **1,2-Amino-methyl-cyclohexane,** b.p. 150°, *benzoyl* derivative, m.p. 147°. **1,3-Amino-methyl-cyclohexane,** b.p. 152°, *benzoyl* derivative, m.p. 163°, obtained by reducing either methyl-cyclohexanone oxime, or *1,3-nitro-methyl-cyclohexane,* b.p. 120°/40 mm., is converted into **methyl-cyclohexyl-hydrazine,** $C_6H_{10}(Me)NHNH_2$ by treating its bromamine with Ag_2O (*Kishner*, C. 1900 I 653). **1,4-Amino-methyl-cyclohexane,** b.p. 151°, *benzoyl* derivative, m.p. 181°. — For the stereochemistry of the acetylated hexahydro-toluidines see *Skita*, Ber. **56**, 1014.

n-Propyl-cyclohexylamine, $C_6H_{11}NH{\cdot}C_3H_7$, b.p. 185°, is obtained from propionitrile and cyclohexanone by catalytic reduction (*Skita*, Mo. **53/54**, 758).

1,2-Diamino-cyclohexane, $C_6H_{10}[1,2](NH_2)_2$, b.p. 183–185°, is obtained by treating the amide of hexahydro-anthranilic acid (p. 130) with sodium hypobromite and then hydrochloric acid. Like the aromatic o-diamines, it combines with benzaldehydes to form benziminazoles (vol. IV) (*Einhorn*, Ann. **295**, 187). It has been resolved into its optical antimers (*Jaeger*,

C. 1936 II 297). **1,3-Diamino-cyclohexane,** b.p. 193°, smells like ethylene diamine and is soluble in water. Nitrous acid decomposes it into nitrogen and dihydrobenzene (*Merling*, Ann. **278**, 39; *Kotz*, J. pr. **80**, 503). The *diacetyl* compound melts at 256°. **1,4-Diamino-cyclohexane,** b.p. 181°, is obtained, like the preceding compound, from the dioxime of the corresponding cyclohexane-dione or from the corresponding nitraniline by reduction (*Skita*, Ber. **52**, 1534).

1,3-Diamino-1-methyl-cyclohexane, *m-diamino-hexahydrotoluene*,

$$C_6H_9(Me)(NH_2)_2,$$

b.p. 85–89°/17 mm.; **1,5-diamino-1,3-dimethyl-cyclohexane,** b.p. 103–105°/27 mm.; **1,5-diamino-1-methyl-3-isopropyl-cyclohexane,** b.p. 115–117°/13 mm. are obtained from the corresponding hydroxylamino-oximes. **1,1-Dimethyl-3,5-diamino-cyclohexane,** b.p. 103–105°/10 mm. (*Harries*, Ann. **328**, 105). See also the ring amines of the terpane and menthane group discussed among the Terpenes.

Cyclohexyl-hydroxylamine, m.p. 140–141°, and its 2-, 3- and 4-methyl-substituted homologues have been prepared by *Vavon* (Bull. **37** (1925), 296) by hydrogenating phenols and cresols in the presence of $NH_2OH \cdot HCl$.

Aminocyclanols have been prepared by *Godchot*, C. r. **196**, 1511.

3. RING KETONES OF THE CYCLOHEXANE SERIES

(a) Ring Ketones of Cyclohexanes.—These compounds form the most easily accessible class of hydroaromatic derivatives and serve as starting materials for the preparation of many other compounds. They have therefore been studied in great detail.

Methods of Preparation: (1) By oxidising the corresponding cyclohexanols with chromic acid, or by leading their vapours over finely divided metallic Cu at 300° (*Sabatier, Senderens*, C. r. **136**, 983). (2) From cyclohexene glycols with dilute acids. (3) By ring synthesis from pimelic acid and its alkyl substitution products by distilling their calcium salts or anhydrides (p. 120; *Blanc*, C. r. **144**, 1356). (4) From the synthetic cyclohexanone carboxylic esters and their alkylation products by hydrolysis and removal of CO_2. (5) By the action of $NaNH_2$ and alkyl halides upon 1,3-methyl-cyclohexanone H-atoms on the carbon atom next to the CO group can be replaced by alkyl (*Haller*, C. r. **140**, 127). (6) Several 1,2-alkyl-cyclohexanones have been obtained from the Mg-compound of 1,2-chloro-cyclohexanone by treatment with alkyl halides (*Bouveault*, C. r. **142**, 1086). (7) Cyclohexanones are formed by an exchange of hydrogen atoms when a cyclohexanol and a phenol are heated in the presence of a catalyst (Swiss Pat. 141,528). (8) Certain 1,3-alkyl-cyclohexanones have been prepared by catalytic reduction of alkyl-dihydroresorcinols (Germ. Pat. 389,815). (9) Dichloro-methyl substituted cyclic ketones of the 2- and 4-series are formed as by-products in the action of $CHCl_3$ on certain phenols (p. 118). The derivatives of the two series behave differently towards *Grignard* compounds (*Auwers*, Ber. **49**, 2389). (10) Methyl-cyclohexene gives methyl-cyclohexanone on treatment with SeO_2 (Germ. Pat. 582,545).

Chemical Reactions: (1) Like the aliphatic ketones the cyclohexanones combine with hydroxylamine, phenylhydrazine, semicarbazide, hydrogen cyanide etc., and in many cases with sodium bisulphite. (2) Reduction gives cyclanols; the rate of reduction is greatest with cyclohexanone itself and decreases with the number of substituents (*Vavon, Couderc*, Belg. **36**, 57). (3) When treated with NaOEt or gaseous HCl, and when heated under pressure, two or three molecules condense together with elimination of water, as in the case of acetone (see cyclohexanone) (*Treibs*, Ber. **61**, 683). (4) Cyclohexanones and benzaldehyde form characteristic mono- or dibenzylidene compounds, condensation taking place with the methylene group next to the CO group (*Wallach*, C. 1908 I 638). (5) With ethyl acetate and sodium they form 1,2-acetyl-cyclohexanones, with diethyl oxalate and sodium ethoxide 1,2-cyclohexanone-oxalic esters (*Kötz*, Ann. **348**, 91), with $NaNH_2$ and CO_2 1,2-cyclohexanone carboxylic acids (*Gardner, Perkin, Watson*, J. **97**, 1746). (6) With PCl_5 unstable dichlorides are first formed; these decompose at once into HCl and chloro-cyclohexenes. (7) Cyclohexanones which contain the grouping $—CO\cdot CH_2—$ are oxidised smoothly by $KMnO_4$ or HNO_3 to adipic acids. For the action of H_2O_2 on cyclic ketones see *Stoll*, Helv. **13**, 142. (8) Some have been converted into ε-lactones by means of *Caro's* acid (*Baeyer*, Ber. **33**, 858). (9) Cyclohexanone oximes are converted into ε-lactams by concentrated H_2SO_4 or PCl_5, and into the nitriles of unsaturated fatty acids by ring fission with P_2O_5 (*Wallach*, Ann. **312**, 173; **346**, 266). (10) Sunlight and water partly convert cyclohexanones into saturated fatty acids and the corresponding unsaturated aldehydes (*Ciamician*, Ber. **41**, 1071). (11) Treatment with alkyl (or allyl) iodides and $NaNH_2$ gives alkyl derivatives in which the H-atoms attached to the two carbons next to the CO-group are replaced. All four H-atoms of the two CH_2-groups can be substituted if the operation is repeated (*Auwers*, Ber. 48, 1226). For the position taken up by the alkyl groups, see *Haller, Cornubert*, C. r. **181**, 81; Bull. **41** (1927), 367, 594. (12) Cyclohexanones condense with C_2H_2 and $NaNH_2$ to give 1-ethinyl-1-cyclanols (p. 101; *Rupe*, Helv. **9**, 672). (13) Cyclohexanones combine with aniline in presence of $ZnCl_2$ to form *Schiff's* bases (*Reddelien*, Ber. **53**, 345). (14) With amyl formate and Na the cyclanones give 2-hydroxymethylene derivatives which react both as enols and as ketones. When their sodium compounds are treated with alkyl halides, the hydroxymethylene group is split off and alkylated ring ketones are formed (*Sen*, J. Ind. chem. Soc. **5**, 609). On reduction they give 2-methyl-ketones, and they condense with hydrazine or semicarbazide to give indazole derivatives (vol. IV; Germ. Pat. 266,405). With hydroxylamine *4,5,6,7-tetrahydro-benzisoxazole* (vol. IV) is formed, with cyano-acetamide *5,6,7,8-tetrahydro-quinoline* (vol. IV), with benzil or desyl chloride (vol. III) *1,2-diphenyl-3,4,5,6-tetrahydrocoumarone* (*Allen*, Can. J. Res. 4, 264). (15) With zinc and α-bromo-fatty esters the ring ketones condense to give cyclohexane-1-ol-1-fatty esters; the free acids give alkylidene cyclohexanes when heated. (16) The cyclic ketones give tertiary ring alcohols with *Grignard* compounds.

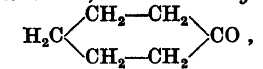
Alkylated cyclanones often occur in stereo-isomeric forms.

For determination of constitution by means of the benzaldehyde compounds see *Cornubert*, C. r. **183**, 294. The same author has studied orientation phenomena in substituted cyclohexanones (Bull. **49** (1931), 1229, 1238, 1468).

	b.p.	d	
Cyclohexanone	156·6–156·8°	0·9471 (22°)	Am. **38**, 996
2-Methylcyclohexanone . .	165°	0·9261 (20°)	J. **1930**, 768
3-Methylcyclohexanone . .	169°	0·9141 (20°)	C. r. **140**, 35
4-Methylcyclohexanone . .	171°	0·9155 (20°)	C. r. **140**, 35
2,2-Dimethylcyclohexanone	170·5–171°	0·9141 (20°)	Ann. **376**, 159; C. r. **170**, 973
3,3-Dimethylcyclohexanone	174°	—	C. r. **144**, 143
3,4-Dimethylcyclohexanone	187°	—	C. r. **142**, 553
2,6-Dimethylcyclohexanone	174°	—	Ber. **28**, 781
2,4-Dimethylcyclohexanone	176·5°	0,9124 (16°)	C. r. **142**, 553
3,5-Dimethylcyclohexanone	182°	0·8994 (17°)	Ann. **297**, 163
2,5-Dimethylcyclohexanone	176°	0·9083 (13°)	C. r. **142**, 553 Ann. **357**, 202
4,4-Dimethylcyclohexanone	m.p. 38–40°	—	—

Other constants of cyclohexanones are given by *Eisenlohr*, C. 1926 I 75.

Cyclohexanone, *pimelic ketone, keto-hexamethylene, "anone",*

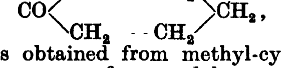


$$\mathrm{H_2C}\begin{matrix}\diagup\mathrm{CH_2-CH_2}\diagdown\\ \diagdown\mathrm{CH_2-CH_2}\diagup\end{matrix}\mathrm{CO},$$

an oil with an odour like peppermint, has been detected in wood spirit oil and, with its homologues, in heavy acetone oil. It can be obtained (1) by the oxidation of cyclohexanol (p. 99); (2) by catalytic reduction of phenol or cyclohexenone (*Kötz,* J. pr. **111,** 373); the mechanism of this hydrogenation, and the intermediate formation of a molecular compound of cyclohexanone and phenol, have been studied by *Vavon* (Bull. **37** (1925), 296); (3) by the distillation of the salts of pimelic acid or of pimelic anhydride (I, 561); (4) by the action of CO_2 on magnesium derivatives of 1,5-dibromopentane (p. 18 and *Grignard,* C. r. **144,** 1358); (5) from nitro-cyclohexane (p. 106) by treatment with glacial acetic acid and zinc dust (*Markovnikov,* Ann. **302,** 18).

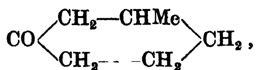
Like camphor, menthol etc. cyclohexanone behaves as a catalyst for the combination of SO_2 and Cl_2 to SO_2Cl_2. On reduction it yields *cyclohexanol,* while nitric acid oxidises it to *adipic acid* (*Rosenlev,* Ber. **39,** 2202; *Holleman,* Rec. **24,** 19). Na-cyanacetic ester combines with cyclohexanone, CO_2 and EtOH being split off, and *Δ^1-cyclohexenyl-acetonitrile,* b.p. 112°/27 mm., formed (*Birch, Kon,* J. **123,** 2444). Condensation with ethyl bromoacetate and zinc produces ethyl 1-cyclohexanol-1-acetate. It condenses with ethyl aceto-acetate and NaOEt with formation of *ethyl Δ^1-cyclohexenyl-aceto-acetate*; the free acid, m.p. 121°, gives a mixture of isomeric cyclohexenyl- and cyclohexylidene-acetones on ketonic hydrolysis (p. 125; *Kon* et al., J. **1928,** 1638). For conversion into β-decalone see *Mannich* et al., Ber. **70,** 355. In presence of NaOEt, CaH_2, or mineral acid, two or three molecules of cyclohexanone condense with the formation of *cyclohexylidene-cyclohexanone,* $(C_6H_8O){:}(C_6H_{10})$ (*W. Hückel,* Ann. **477,** 119), *dicyclohexylidene-cyclohexanone,* $(C_6H_{10}){:}(C_6H_6O){:}(C_6H_{10})$, b.p. 214–217°, and *dodecahydro-triphenylene* (*Mannich,* Ber. **40,** 153; *Vorländer,* ib. **59,** 2085). For electrochemical oxidation see *Pirrone,* Gazz. **66,** 244. Illumination of an aqueous-alcoholic solution of cyclohexanone gives caproic acid and Δ^5-hexene aldehyde. With an excess of N_3H cardiazole, a bicyclic compound containing a tetrazole ring, is formed (*Schmidt,* Ber. **57,** 714). Cyclohexanone *oxime,* m.p. 87–88° (*Bousquet,* Org. Synth. **11,** 56), is transformed by conc. H_2SO_4 into ε-capro-lactam (I, 451). *Semicarbazone,* m.p. 155° (*Kotz,* J. pr. **111,** 398). Its *phenylhydrazone,* m.p. 74–77°, loses ammonia when treated with mineral acids and gives tetrahydro-carbazole (vol. IV) (*Baeyer,* Ann. **278,** 100). For condensation with aromatic aldehydes see *Vorlander,* Ber. **58,** 132; **59,** 2078; *Cornubert,* C. r. **186,** 1126. With benzaldehyde cyclohexanone condenses to a *mono-* and a *dibenzylidene* compound, $PhCH{:}(C_6H_8O)$, m.p. 54·6° (*Wallach,* Ber. **40,** 71), and $PhCH{:}(C_6H_6O){:}CHPh$, m.p. 117–118° (*Vorländer,* Ber. **59,** 2081). Under special conditions it is possible to isolate a *mono-* and a *dialdol,* m.ps. 102° and 162°, which are intermediate products (*Wallach,* C. 1908 I 638). With nitrous acid *di-isonitroso-cyclohexanone* $HON{:}(C_6H_6O){:}NOH$, m.p. 200° decomp. is obtained (*Borsche,* C. 1909 II 1549). Chlorine and bromine react readily to give *1,2-chloro-* and *1,2-bromo-cyclohexanones,* b.p. 82°/10 mm. and b.p. 89°/14 mm. Excess of Br_2 gives a tetrabromo compound, m.p. 120°, which, on heating, loses HBr and forms 2,6-dibromophenol (*Kotz,* Ann. **343,** 40).

2-Methyl-cyclohexanone,



$$\mathrm{CO}\begin{matrix}\diagup\mathrm{CHMe-CH_2}\diagdown\\ \diagdown\mathrm{CH_2-CH_2}\diagup\end{matrix}\mathrm{CH_2},$$

m.p. 165°, *semicarbazone* m.p. 195–196°, is obtained from methyl-cyclohexanol, or from hydroxymethylene-cyclohexanone, or from cyclohexane with CO and $AlCl_3$. In the last reaction, ring contraction (p. 47) does not take place, but a CH_2-group is extruded into a side chain and is replaced by a CO-group (*Hopff,* Ber. **65,** 483). For the phenylation and benzylation of 2-methylcyclohexanone see *Cornubert,* C. r. **186,** 1126.



3-Methyl-cyclohexanone, $\mathrm{CO}\Big\langle\begin{matrix}\mathrm{CH_2-CHMe}\\ \mathrm{CH_2-CH_2}\end{matrix}\Big\rangle\mathrm{CH_2}$, has been obtained in an optically active dextrorotatory form, $[\alpha]_D + 12{\cdot}5^\circ$, by decomposition of natural pulegone (*Tiemann*, Ber. **30**, 23; J. pr. **61**, 477). It occurs in American pennyroyal oil and in Japanese peppermint oil (*Kremers*, J. Biol. Ch. **50** (1921), 31).

On oxidation with HNO_3 both α- and β-methyl-adipic acids are formed (*Markovnikov*, Ann. **336**, 299). Its *oxime*, m.p. 44°, is transformed by conc. H_2SO_4 into a mixture of β- and δ-methyl-ε-caprolactam (*Wallach*, Ann. **346**, 253). For its conversion into m-cresol, see *Wallach*, Ber. **32**, 3338. The action of $NaNH_2$ and the appropriate alkyl iodide on 3-methyl-cyclohexanone gives **1-methyl-4-ethyl-** and **1-methyl-4-propyl-cyclohexanone-3,** b.ps. 84°/18 mm. and 98°, and many homologous cyclohexanones have been prepared (*Cornubert*, C. r. **186**, 441); see synthesis of menthone, p. 230. The active ketone condenses, partly in its enolic form, with ethyl succinate (*Stobbe*, J. pr. **89**, 341) and with aromatic bases (*v. Braun*, Ann. **507**, 27).

The Germ. Pat. 519,470 describes the use of cyclohexanone and methylcyclohexanone for purifying glycerol. A condensation product of the dihydro-1,3-dioxol type, which easily dissociates, is formed as an intermediate. For the action of hydrazine hydrate upon cyclohexanone and methyl-cyclohexanones see *Mailhe*, C. r. **174**, 465, and for the ultraviolet absorption of alkyl-cyclohexanones see *Ramart-Lucas*, Bull. **53** (1933), 744.

4-Methylcyclohexanone, b.p. 170°, *oxime* m.p. 37–39°, *semicarbazone* m.p. 197° is obtained from γ-methylpimelic acid by distillation with CaO (*Einhorn, Ehret*, Ann. **295**, 186), from 4-methylcyclohexanol by catalytic oxidation (*Sabatier, Mailhe*, C. r. **140**, 552), and from 4-methyl-1-cyclohexanol-1-carboxylic acid by treatment with conc. H_2SO_4 at —10° (*Perkin*, J. **89**, 836).

2-Chloro-cyclohexanone, m.p. 22–23°, is prepared, together with **dichlorocyclohexanone,** m.p. 72–73°, from cyclohexanol and chlorine (*Meyer*, Helv. **16**, 1291; *Bartlett*, Am. **56**, 1990). **2-Chloro-2-methyl-cyclohexanone,** b.p. 78–79°/14 mm., is obtained from 2-methyl-cyclohexanone with chloro-urea. **2-Chloro-4-methyl-cyclohexanone,** cis b.p. 80–82°/12 mm., trans b.p. 110–112°/12 mm., is obtained by chlorinating 4-methyl-cyclohexanone in the presence of water and $CaCO_3$ (*Godchot*, C. r. **180**, 295; **181**, 919; Bull. **39** (1926), 83).

2,2-Dimethyl-cyclohexanone is formed from 1-isopropyl-cyclopentane-1,6-diol (p. 56) by pinacolin rearrangement and simultaneous ring enlargement (*Meerwein* and *Unkel*, Ann. **376**, 152).

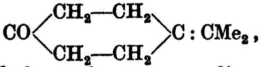
Stereoisomeric and optically active forms of 2,5-, 2,6- and 3,5-dimethyl-cyclohexanones have been studied by *Skita*, Ber. **56**, 2235 and *v. Braun*, ib. **60**, 2442.

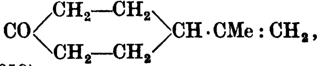
3,5,5-Trimethyl-cyclohexanone, *dihydro-isoacetophorone* (*Pringsheim*, Angew. **40**, 1392), b.p. 53·5–54°/11 mm., *semicarbazone* m.p. 202°, occurs in heavy acetone oil and has been obtained from dihydro-isoacetophorol, the reduction product of iso-acetophorone, by oxidation with chromic acid. For transformation of the oximes, see *Wallach*, Ann. **346**, 256. **2,4,4-Trimethyl-cyclohexanone,** b.p. 191°, b.p. 61°/11 mm., is obtained from 2,4,4-trimethyl-cyclohexenone (p. 115) (id. ib. **324**, 97); it too has been found in heavy acetone oil (*Pringsheim*, Ber. **58**, 414). **2,2,6-Trimethyl-cyclohexanone,** b.p. 66–67°/10 mm., occurs in the essential oil of labdanum (*Masson*, C. r. **154**, 517). **3,6,6-Trimethyl-cyclohexanone**: see pulenone (p. 236).

2-n-Propyl-cyclohexanone, b.p. 83–84°/13 mm., *semicarbazone* m.p. 133·5–134° decomp., is prepared from o-allyl-phenol by hydrogenation, and from the alcohol with dichromate (*Vavon*, Bull. **41** (1927), 1638). **3-Isopropyl-cyclohexanone,** b.p. 94°/15 mm., *semicarbazone* m.p. 187°, is obtained from isopropyl-dihydroresorcinol (p. 112) by catalytic reduction (Germ. Pat. 389,815).

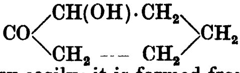
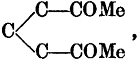
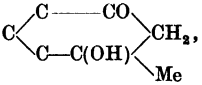
Cyclohexanones with aromatic substituents have been prepared by *Cornubert*, Bull. **2** (1935), 195.

Cyclic ketones with unsaturated side chains: **2-Allyl-cyclohexanone,** b.p. 94°/16 mm.; **2-methyl-2-allyl-cyclohexanone,** b.p. 96–97°/14 mm., can be obtained from the ketones with allyl halide + $NaNH_2$ (*Cornubert*, C. r. **158**, 1900). *Polyallyl-cyclohexanones* see ib.

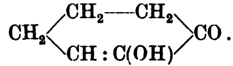
1,4-Isopropylidene-cyclohexanone, , b.p. 220°, *semicarbazone* m.p. 205°, is obtained from the corresponding carboxylic ester (p. 139) (*Perkin, Simonsen*, J. **91**, 1736) and from sabinene by oxidation with CrO_2Cl_2 (*Henderson* et al., J. **121**, 2721).

1,4-Isopropenyl-cyclohexanone, , b.p. 184–186°/300 mm. (*Perkin*, J. **85**, 659).

2-Methylene-5-isopropyl-cyclohexanone-1, *santolinenone*, see Terpenes (p. 237).

Ring-ketols: **1,2-Cyclohexanolone,** , m.p. 130° (*Bergmann*, Ann. **448**, 60), sublimes very easily; it is formed from 1,2-chloro-cyclohexanone with alkalies. It yields adipic acid on oxidation with $KMnO_4$ (*Bouveault*, C. r. **142**, 1086; *Kotz*, J. pr. **80**, 488). **4 (or 6)-Methyl-1,2-cyclohexanolone,** $MeC_6H_8O(OH)$, b.p. 86°/12 mm., is obtained from methyl-bromo-cyclohexanone (*Zelinsky*, Ber. **35**, 2695). **3-Methyl-1,2,3-cyclohexanone-diol,** $MeC_6H_7O(OH)_2$, m.p. 52°, is formed from synthetic methyl-cyclohexenone (p. 115) and also from $\Delta^{1,3}$-dihydro-toluene (p. 97) by oxidation with $KMnO_4$; on boiling with dilute sulphuric acid it yields 1-methyl-cyclohexane-2,3-dione (*Harries*, Ber. **35**, 1176). 1,3-Cyclohexanolones must be assumed as intermediate products in the formation of cyclohexenones from 1,5-diketones , some of which should perhaps be given the formula , (p. 114) (*Rabe*, Ann. **323**, 83; *Knoevenagel*, Ber. **36**, 2218).

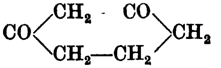
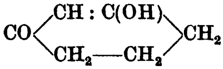
Cyclohexane-diones, diketo-hexamethylenes. — The three isomeric cyclohexane-diones predicted by theory are all known.

1,2-Cyclohexane-dione, *o-diketo-hexamethylene*, m.p. 38–40°, is obtained from cyclohexanone by the action of KOH on the dibromo compound; *dioxime* m.p. 189–190°. It also reacts in the keto-enol form as the simplest "diosphenol" (p. 237): .

1-Methyl-2,3-cyclohexane-dione, m.p. 64–65°, from methyl-cyclohexanone-diol (see above) by loss of water, smells strongly of quinone (*Harries*, Ber. **35**, 1178).

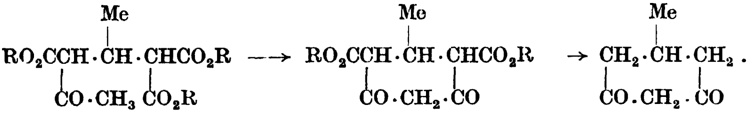
The dioximes of 1,2-cyclohexane-dione and of its homologues are cyclic homologues of glyoxime and form sparingly soluble, coloured salts with certain metals of the transitional groups, especially with Ni. The sensitivity of the red colour with Ni is 1:10⁶ (*Wallach*, Ann. **437**, 148; *Franz*, ib. 165).

1,3-Cyclohexane-dione, *dihydro-resorcinol, m-diketo-hexamethylene*,

 or ,

m.p. 104–106° decomp., behaves as a weak acid, and should thus be regarded as an unsaturated cyclic ketonic alcohol. It is formed when Na amalgam is added to a boiling aqueous solution of resorcinol through which a stream of CO_2 is passing. It may be synthesised by condensing ethyl γ-acetyl-butyrate with NaOEt. Dihydroresorcinol is readily soluble in water, alcohol and chloroform, but only slightly in ether. It has an acid reaction and decomposes the alkali and alkaline earth carbonates. It can be esterified directly with alcohol and HCl. On the other hand, it forms a *dioxime*, $C_6H_8(NOH)_2 + 2H_2O$, m.p. (anh.) 154–157°, which gives 1,3-diamino-cyclohexane on reduction. Dihydroresorcinol combines with HCN to give the dinitrile of 1,3-dihydroxy-cyclohexane-1,3-dicarboxylic acid (p. 145; *Merling*, Ann. **278**, 20). With PCl_3 it gives chloro-cyclohexenone C_6H_7OCl, b.p. 104°/24 mm., and with PCl_5 dichloro-cyclohexadiene $C_6H_6Cl_2$, b.p. 89°/29 mm. (*Crossley*, J. **83**, 494); with bromine 2-bromo-dihydroresorcinol, $C_6H_7O_2Br$, is formed. Dihydroresorcinol is decomposed by NaOBr or bleaching powder to glutaric acid and bromoform or chloroform, and when heated with aqueous baryta to 150–160°, it is hydrolysed to γ-acetyl-butyric acid (*Vorländer*, Ann. **294**, 269; **308**, 184; **322**, 239, 245).

Just as dihydroresorcinol is formed from γ-acetyl-butyric ester (see above), so its homologues are obtained by condensation of other δ-keto-carboxylic esters. These are prepared by combining ethyl sodio-malonate with α,β-unsaturated ketones or alkylidene-aceto-acetic esters, or ethyl sodio-aceto-acetate with α,β-unsaturated carboxylic esters. For example, when ethylidene-aceto-acetic ester is condensed with malonic ester by means of NaOEt, the product hydrolysed and CO_2 eliminated, **methyl-dihydroresorcinol** is formed (*Knoevenagel*, Ann. **289**, 137; *Vorlander*, ib. **294**, 253).

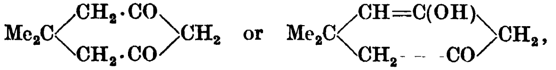


$$RO_2C\underset{CO\cdot CH_3}{CH}\cdot\overset{Me}{CH}\cdot\underset{CO_2R}{CHCO_2R} \longrightarrow RO_2C\underset{CO\cdot CH_2\cdot CO}{CH\cdot\overset{Me}{CH}\cdot CH}CO_2R \rightarrow \underset{CO\cdot CH_2\cdot CO}{CH_2\cdot\overset{Me}{CH}\cdot CH_2}\,.$$

Substituted dihydroresorcinols: see *Gilling*, J. **103**, 2029; *Boyd*, ib. **117**, 1383. **Isopropyl-dihydroresorcinol**, $Me_2CH{\cdot}C_6H_7O_2$, m.p. 82° (*Crossley*, J. **81**, 675). **Phenyl-dihydroresorcinol**, $PhC_6H_7O_2$, m.p. 184° decomp. **1,2-Diphenyl-dihydroresorcinol**, m.p. 160°, is obtained from phenyl-acetic ester, benzylidene-acetone and NaOEt (*Borsche*, Ber. **42**, 4498).

Styryl-dihydroresorcinol, $(PhCH{:}CH)C_6H_7O_2$, from cinnamylidene-acetone and Na-malonic ester, is converted by bleaching powder into styryl-glutaric acid (*Vorlander*, Ann. **345**, 206).

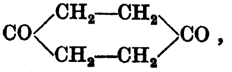
5,5-Dimethyl-dihydroresorcinol,



m.p. 148–150° decomp., obtained from mesityl oxide and sodio-malonic ester, gives with NaOBr or bleaching powder β,β-dimethyl-glutaric acid (*Komppa*, Ann. **368**, 135). When reduced by *Clemmensen's* method it undergoes ring contraction to some extent, 2,4,4-trimethyl-cyclopentanone being found among the products (*Linstead*, J. **1935**, 1063). 5,5-Dimethyl-hydro-resorcinol, also known as *methone, dimethone* or *dimedone*, is often used for isolating aldehydes, with which it condenses to give products of the formula $R{\cdot}CH[CH{:}(COCH_2)_2{:}CMe_2]_2$ (*Vorländer*, Z. analyt. Ch. **77** (1929), 241; *Klein*, C. 1930 I 2085). For its condensation with SeO_2 see *Stamm*, Ber. **66**, 1558. Halogen derivatives see *Vorlander*, Ann. **322**, 239. For its conversion into 1,1-dimethyl-di- (and -tetra-) hydrobenzene see *Crossley*, J. **93**, 629. **Trimethyl-dihydroresorcinol**, m.p. 100°, id. J. **79**, 143. For further reactions of the dihydroresorcinols see *Friedmann*, J. pr. **146**, 65, 71, 79.

The homologous dihydroresorcinols show the reactions of dihydro-resorcinol itself, and behave as diketones and also as unsaturated hydroxy-ketones.

1,4-Cyclohexanedione, *tetrahydro-quinone, p-diketo-hexamethylene*,



m.p. 78°, results from hydrolysing ethyl succino-succinate with conc. sulphuric acid, or with aqueous alcoholic HCl, CO_2 being eliminated

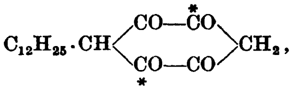
(*Baeyer*, see p. 83). When ethyl succino-succinate is heated with MeOH or EtOH to 200°, acetals of 1,4-cyclohexanedione are formed: methyl-acetal, m.p. 81°, ethyl-acetal m.p. 89° (*Stollé*, Ber. **34**, 1344). 1,4-Cyclohexanedione is also produced in small quantities in the distillation of calcium succinate. It unites with sodium bisulphite, and forms a *dioxime*, m.p. 192°; the latter is converted by chlorine into *1,4-dichloro-1,4-dinitroso-cyclohexane* $(ON)CCl(CH_2.CH_2)_2CCl(NO)$, deep-blue crystals m.p. 108°, transformed by AcOH + HCl into a colourless form melting at 128–130° decomp. These are cis-trans isomers, the blue form, in which the two nitroso groups are too far apart to interact, being the trans compound (*Piloty*, Ber. **35**, 3101). With benzaldehyde and HCl 1,4-cyclohexanedione unites to form benzyl-hydroquinone (*Stollé*, Ber. **37**, 3486). It forms quinitol on reduction; see also α,α′-dihydroxy-hexahydro-terephthalic acid (p. 145).

2,5-Dimethyl-1,4-cyclohexanedione, m.p. 93°, is obtained from 1,4-dimethyl-succino-succinic ester (*Baeyer*, Ber. **25**, 2121).

4,6,6-Trimethyl-4-acetyl-1,3-cyclohexanedione, *angustione*, b.p. 129°/15 mm., is a cyclic diketone with substituents which occurs naturally in the essential oil of *Backhousia angustifolia*, together with dehydro-angustione. On oxidation it yields *l*-α,α,γ-trimethyl-glutaric acid (*Gibson*, J. **1930**, 1184).

Cyclohexane-polyones. — Phloroglucinol yields derivatives, some of which are related in structure to 1,3,5-trihydroxy-benzene, and others to cyclohexane-1,3,5-trione. They will be discussed at the end of the section dealing with pyrogallol and hydroxy-hydroquinone, together with the hexaalkyl derivatives of phloroglucinol (vol. III).

1-Dodecyl-cyclohexane-2,3,5,6-tetrone, *embelin*,



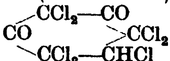
$$C_{12}H_{25}\cdot CH\begin{array}{l}\diagup CO-\overset{*}{C}O\diagdown\\ \diagdown CO-\underset{*}{C}O\diagup\end{array}CH_2,$$

forms orange red crystals melting at 143°. It occurs in the fruit of the Indian shrub *Embelia ribes*. The two CO-groups* can enolise (*Narghund*, J. Ind. chem. Soc. **8**, 237). It is used as an anthelmintic; cf. Natural Substances p. 422.

Hexaketo-cyclohexane or *triquinoyl*, $C_6O_6 + 8H_2O$, is described among the quinones (vol. III).

Halogen substitution products of the ring-ketones of cyclohexane are formed in the continued action of chlorine and bromine on phenols, quinones and hydroxy-quinones. Many of the ketochlorides readily rearrange into halogen keto-pentene derivatives, and decompose into highly chlorinated aliphatic compounds, such as ketones, ketonic acids, and fatty acids (see vol. III).

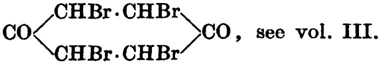
Heptachloro-1,3-cyclohexanedione, *heptachloro-resorcinol*,



$$CO\begin{array}{l}\diagup CCl_2-CO\\ \diagdown CCl_2-CHCl\end{array}\!\!>CCl_2,$$

m.p. 50°, b.p. 170°/25 mm., is obtained from resorcinol (vol. III) and Cl_2 in chloroform. For its decomposition products see vol. III.

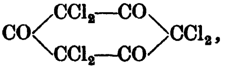
2,3,5,6-Tetrabromo-cyclohexanedione, *quinone tetrabromide*,



$$CO\begin{array}{l}\diagup CHBr\cdot CHBr\diagdown\\ \diagdown CHBr\cdot CHBr\diagup\end{array}CO,$$

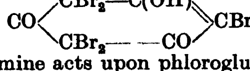
see vol. III.

Hexachloro-1,3,5-cyclohexanetrione,



$$CO\begin{array}{l}\diagup CCl_2-CO\diagdown\\ \diagdown CCl_2-CO\diagup\end{array}CCl_2,$$

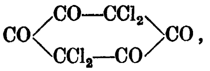
m.p. 48°, b.p. 268°, is formed by the action of chlorine on phloroglucinol in $CHCl_3$ (*Zincke*, Ber. **22**, 1473). Its decomposition is dealt with in vol. III. **Pentabromo-cyclohexenol-dione,**



$$CO\begin{array}{l}\diagup CBr_2-C(OH)\diagdown\\ \diagdown CBr_2-\ -CO\diagup\end{array}\!\!\!>CBr + H_2O,$$

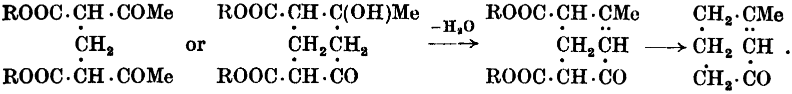
m.p. 119° decomp., is produced when bromine acts upon phloroglucinol in water. It forms amber coloured crystals and is a strong acid.

Hexabromo-cyclohexatrione, $C_6Br_6O_3$, m.p. 147° (*Zincke*, Ber. **23**, 1729; **24**, 912). **Tri- and tetra-chloro-cyclohexane-tetrones,**



are obtained from chloranilic acid and chlorine. The corresponding bromine derivatives are made from bromanilic acid (*Landolt*, Ber. **25**, 845).

(b) Ring Ketones of Cyclohexenes. — Ketones of this class have been isolated from heavy acetone oil, together with saturated ring ketones (*Pringsheim*, Angew. **40**, 1390). They have been prepared by *Kotz* (J. pr. **80**, 490) by removing water from ring-ketols by means of anhydrous oxalic acid, or removing hydrogen halide from halogenated ring ketones, or by dry distillation of cyclanonyl xanthates. Their synthesis has been achieved by *Rabe* (Ann. **332**, 22; cp. vol. III) by condensing ethyl aceto-acetate, acetone-dicarboxylate or analogous compounds with alkylene di-iodides, such as methylene iodide, or with aldehydes in the presence of small quantities of bases like diethylamine or piperidine. 1,5-Diketo-carboxylic esters, e.g. methylidene-, ethylidene-, isobutylidene-diaceto-acetic esters and methylene-bis-acetone-dicarboxylic esters, are formed in this process. Some of these compounds probably have a cyclic structure and should be formulated as esters of cyclohexanolone-dicarboxylic acids. When treated with dilute ethereal HCl they lose water and pass into carboxylic esters of Δ^2-cyclohexenones; finally, by action of alkalies or dilute acids, they are hydrolysed to give the ketones themselves, with loss of CO_2 (*Knoevenagel*, Ann. **289**, 131):



$$\begin{matrix}\mathrm{ROOC\cdot CH\cdot COMe}\\ \mathrm{CH_2}\\ \mathrm{ROOC\cdot CH\cdot COMe}\end{matrix}\quad\text{or}\quad\begin{matrix}\mathrm{ROOC\cdot CH\cdot C(OH)Me}\\ \mathrm{CH_2CH_2}\\ \mathrm{ROOC\cdot CH\cdot CO}\end{matrix}\xrightarrow{-H_2O}\begin{matrix}\mathrm{ROOC\cdot CH\cdot CMe}\\ \mathrm{CH_2CH}\\ \mathrm{ROOC\cdot CH\cdot CO}\end{matrix}\longrightarrow\begin{matrix}\mathrm{CH_2\cdot CMe}\\ \mathrm{CH_2\ CH}\\ \mathrm{CH_2\cdot CO}\end{matrix}.$$

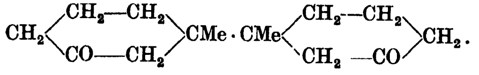
From acetyl-acetone with aldehydes, tetraketones,

$$(MeCO)_2CH\cdot CHR\cdot CH(COMe)_2,$$

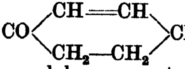
are obtained, which by double ring closure yield *bicyclic* systems whose structure has not yet been ascertained (*Knoevenagel*, Ber. **36**, 2136).

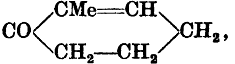
From the nitrosochlorides of some cyclohexenes Δ^2-cyclohexenones have been prepared by loss of HCl, by means of NaOEt or NaAc + Ac_2O and hydrolysis of the resulting oximes with oxalic acid or phthalic anhydride. A methyl-cyclohexenone has been obtained by heating methyl-cyclohexene with SeO_2 (Germ. Pat. 582,545).

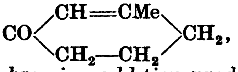
With sodium and alcohol Δ^2-cyclohexenones are reduced to the saturated cyclohexanols (p. 98). If, however, sodium amalgam in acid solution is used, two molecules unite and derivatives of *diketo-perhydro-diphenyl* are formed. Thus, 3-methyl-Δ^2-cyclohexenone gives



By the action of two molecules of hydroxylamine ketoximes are first formed and then, by addition, hydroxylamino-oximes; from 3-methyl-Δ^2-cyclohexenone e.g. 3-methyl-3-hydroxylamino-cyclohexanone-oxime (*Harries*, Ber. **32**, 1315). Conversion of the dibromides of alkyl and aryl substituted cyclenones into phenols: *Petrov*, Ber. **63**, 898.

Δ^2-Cyclohexenone,  b.p. 63°/14 mm, is prepared from 1,2-Cl- or 1,2-Br-cyclohexanone (p. 110) by boiling with aniline or, together with Δ^2-cyclohexenol, from cyclohexene and O_2 in the presence of colloidal Os-salts (*Kotz*, J. pr. **80**, 491; **111**, 373); also from Δ^2-cyclohexenol or chloro-Δ^2-cyclohexene by oxidation with chromic mixture (*Courtot*, Bull. **45** (1929), 286), and from 1,2-cyclohexanolone with anhydrous oxalic acid. Its unstable dibromide loses 2 HBr easily and is converted into phenol. The *oxime* melts at 75° and yields aniline on boiling with acetic anhydride; *hydroxylamino-oxime*, m.p. 50° (*Kötz*, J. pr. **80**, 501). A compound derived from **Δ^3-cyclohexenone,** b.p. 208°, *semicarbazone* m.p. 254°, is thought to be the cause of the smell of normal urine ("urinod") (*Dehn*, Am. **36**, 2136; *Anderson*, J. Biol. Ch. **26**, 409).

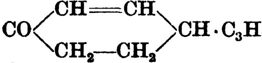
2-Methyl-Δ^2-cyclohexenone,  $CO\left<\begin{matrix}CMe=CH\\CH_2-CH_2\end{matrix}\right>CH_2$, b.p. 179°, *semicarbazone* m.p. 193°, is obtained from the nitrosochloride of Δ^1-methylcyclohexene (*Meerwein*, Ann. **359**, 303), or from 2-chloro-2-methylcyclohexanone-1 with quinoline. With MeMgI it gives *cantharenol*, 1,2-Δ^2-dimethyl-cyclohexenol-1 (p. 97).

3-Methyl-Δ^2-cyclohexenone,  $CO\left<\begin{matrix}CH=CMe\\CH_2-CH_2\end{matrix}\right>CH_2$, b.p. 200°, is a mobile liquid of pleasant odour. Its bromine addition product decomposes spontaneously into HBr and m-cresol. Two isomeric forms seem to exist, one miscible with water and another difficultly soluble in it. They show the same chemical behaviour and both are oxidised to γ-acetyl-butyric acid by $KMnO_4$. The *oxime*, m.p. 89° gives m-toluidine on boiling with acetic acid. The *hydroxylamino-oxime*, m.p. 84°, gives a nitroso-oxime on oxidation with mercuric oxide. When heated with conc. KOH, 3-methyl-Δ^2-cyclohexenone is converted into a polymer, m.p. 113°, which resembles an aldol. It combines with ethyl sodio-aceto-acetate to form a 1,5-diketo-carboxylic ester, which undergoes ring closure and gives a bicyclic ketonic alcohol (*Knoevenagel*, Ber. **32**, 423; Ann. **297**. 142; *Rabe*, Ber. **37**, 1671; **40**, 2482; *Wolff*, Ann. **322**, 382).

5-Methyl-Δ^2-cyclohexenone-1, b.p. 170°, *semicarbazone* m.p. 182°, has been prepared by heating with quinoline the mixture of stereoisomeric 4-chloro-ketones obtained by chlorinating 1,3-methyl-cyclohexanone (*Godchot*, Bull. **39** (1926), 83).

2-Methyl-3-ethyl-Δ^2-cyclohexene-1-one, b.p. 105°/19 mm., is formed from dipropionyl-propane by heating with aqueous alkalies or acids.

2-Isopropyl-Δ^2-cyclohexene-1-one, *semicarbazone*, m.p. 165—166° (*Meerwein*, J. pr. **104**, 289). The *oxime*, m.p. 72°, was prepared by *Wallach* (Ann. **360**, 69) by treating the nitrosochloride of 1-isopropyl-Δ^1-cyclohexene with sodium acetate or piperidine. The *nitrosochloride*, m.p. 128·5°, is formed when water is eliminated from 1,1-dimethyl-cycloheptanol-2 and the resulting hydrocarbon is treated with glacial acetic acid, $NaNO_2$ and HCl.

4-Isopropyl-Δ^2-cyclohexenone,  $CO\left<\begin{matrix}CH=CH\\CH_2-CH_2\end{matrix}\right>CH\cdot C_3H_7$, b.p. 99°/10 mm., semicarbazone m.p. 185° dec. The laevorotatory form occurs in the pine needle oil from *Pinus montana* (*P. pumilio*) and in the oil from *Eucalyptus cneorifolia* (*Wienhaus*, *Schimmel* Ber. Jub.-Ausg. **1929**, 233; *Cahn*, *Penfold*, *Simonsen*, J. **1931**, 1366; *Berry*, *Macbeth* and *Swanson*, J. **1937**, 986). It is formed, together with 4-isopropylidene-cyclohexanone' when sabinaketone (p. 240) and nopinone (p. 262) are heated with dilute H_2SO_4, and by autoxidation of β-phellandrene (p. 212). It polymerises very easily, especially when alkali is present. With MeMgI, water is split off and α-phellandrene (p. 212) is formed (*Meerwein*, Ann. **359**, 270).

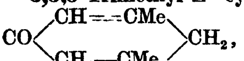
5-Isopropyl-Δ^2-cyclohexene-1-one, b.p. 94°/15 mm., and especially its 3-methyl derivative, b.p. 114—115°/12 mm., which were prepared by *Knoevenagel* (Ber. **26**, 1089) from ethyl isobutylidene-diaceto-acetate with alkali or acid, are used as stimulants of respiration and circulation, under the name of "*hexetone*" (*Gottlieb*, C. 1924 I 1232). The physiological effect depends on the isopropyl group being attached to the six-membered ring in the 3-position to the CO; the presence of the double bond is not essential (*Wede-*

kind, Angew. **38**, 315). — For the resolution into optical antimers see *Wegler*, C. 1936 I 53.

3,5-Dimethyl-Δ^2-cyclohexenone, b.p. 211°, is obtained by the action of dilute H_2SO_4 on ethyl ethylidene-diacetoacetate. Its dibromide easily passes into symm. xylenol (vol. III) (*Wallach*, Ann. **281**, 111; *Rabe, Elze*, ib. **323**, 100); its *oxime*, m.p. 68–74°, when heated with HCl, gives symm. xylidine (*Wolff*, Ann. **322**, 381).

5,5-Dimethyl-Δ^2-cyclohexenone, b.p. 88·5°/32 mm., is obtained by reducing with zinc dust dimethyl-chloro-cyclohexanone, the product of the action of PCl_3 upon dimethyl-dihydroresorcinol. With permanganate it gives α-hydroxy-β,β-dimethyl-glutaric acid and as.-dimethyl-succinic acid (*Crossley*, J. **91**, 78).

3,5,5-Trimethyl-Δ^2-cyclohexenone, iso-acetophorone, isophorone, $C_9H_{14}O$,

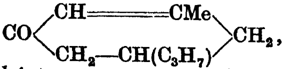


$\mathrm{CO}\!<\!\begin{matrix}\mathrm{CH{=}CMe}\\ \mathrm{CH_2{-}CMe_2}\end{matrix}\!>\!\mathrm{CH_2}$, b.p. 89°/10 mm., *semicarbazone* m.p. 181–182°, has been detected in heavy acetone oil (*Pringsheim*, Angew. **40**, 1390), and is produced in the condensation of acetone by lime, NaOEt or $NaNH_2$, or of mesityl oxide with ethyl sodio-aceto-acetate, followed by hydrolysis and elimination of CO_2 from the isophorone-carboxylic ester first formed (p. 139), and also by heating dimethyl-cyclohexenone-acetic ester in alcoholic solution with lime (*Freund*, Ber. **35**, 2322). It is isomeric with phorone, camphorphorone, iso-camphorone, nopinone, camphenilone and the fencho-camphorones (see below). When reduced with Na + EtOH it forms *dihydroisophorol*, $C_9H_{17}(OH)$, which by loss of water yields trimethyl-cyclohexene, and by the reduction of its iodide trimethyl-cyclohexane (*Knoevenagel*, Ann. **297**, 194). When it is oxidised with permanganate, the ring is opened and several acids are obtained: γ,γ-dimethyl-α,ε-diketo-heptylic acid $C_9H_{14}O_4$, γ-acetyl-β,β-dimethyl-butyric acid $C_8H_{14}O_3$, and as. dimethyl-succinic acid (*Crossley*, J. **95**, 19). Isophorone gives two isomeric *oximes* b.ps. 75° and 100°, which are converted into 1-amino-3,4,5-trimethyl-benzene on heating with HCl to 170° (*Bredt*, Ann. **299**, 165; *Karp*, ib. 193; *Wolff*, Ann. **322**, 379).

Besides isophorone, the condensation products of acetone contain more highly condensed ketones, the so-called **xylitones,** $C_{12}H_{18}O$, probably formed by condensation of a further molecule of acetone with isophorone. The xylitones produced by different condensing agents, such as lime, NaOEt, and HCl, all seem to differ from one another. An isomeric xylitone, b.p. 133°/12 mm., not identical with any of the others, has been obtained by the addition of ethyl sodio-aceto-acetate and phorone.

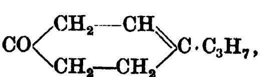
2,4,4-Trimethyl-Δ^2-cyclohexenone, b.p. 195–196°, is formed from α-cyclogeranic acid (p. 207) and HOI, together with the corresponding alcohol, b.p. 193°/760 mm., which is oxidised by chromic acid to the ketone (*Bougault*, C. r. **150**, 397), and also from α-cyclogeraniolene nitrosochloride (p. 95) (*Wallach*, Ann. **324**, 97).

3-Methyl-5-isopropyl-Δ^2-cyclohexenone,



$\mathrm{CO}\!<\!\begin{matrix}\mathrm{CH{=}CMe}\\ \mathrm{CH_2{-}CH(C_3H_7)}\end{matrix}\!>\!\mathrm{CH_2}$, b.p. 244°. Its dibromide is readily transformed into symm. carvacrol (vol. III) (*Knoevenagel*, Ber. **26**, 1089; **27**, 2347; Ann. **288**, 357). **3-Methyl-5-isobutyl- and 3-methyl-5-hexyl-Δ^2-cyclohexenones,** b.ps. 147°/22 mm. and 167°/22 mm. (id. Ann. **288**, 336, 344).

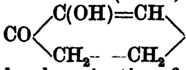
4-Isopropyl-Δ^3-cyclohexenone



$\mathrm{CO}\!<\!\begin{matrix}\mathrm{CH_2{-}CH}\\ \mathrm{CH_2{-}CH_2}\end{matrix}\!>\!\mathrm{C{\cdot}C_3H_7}$, b.p. 95°/12 mm., *semicarbazone*, m.p. 170°, is formed from the HCl addition product of sabinaketone (p. 240) by heating with dimethylaniline. Mineral acids transform it into the Δ^2-ketone. With MeMgI it yields terpinenol-1 (*Wallach*, Ann. **362**, 280). **2,2,3-Trimethyl-Δ^3-cyclohexenone,** b.p. 85–90°/11 mm., and **2,2,3,6-tetramethyl-Δ^3-cyclohexenone,** b.p. 90°/11 mm., are related in structure to irone. The first is formed from 2,6-dimethyl-3-hexene-

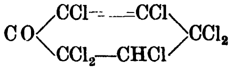
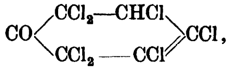
2,6-dicarboxylic ester by ring closure with NaOEt; the latter by a similar reaction in the presence of MeI (*Ruzicka*, Helv. **2**, 144).

4-Methyl- and 2,4-dimethyl-Δ^4-cyclohexenones, b.ps. 192° and 194°, are found among the ketones of wood-tar (*Béhal*, C. r. **182**, 342).

Δ^2-Cyclohexene-2-ol-one,  m.p. 38–40°, is obtained from cyclohexanone by bromination followed by treatment with KOH. *Phenylurethane*, m.p. 124°. It can react as a 1,2-diketone, see p. 111 2-Methyl-cyclohexanone yields the corresponding methyl derivative (*Wallach*, Ann. **437**, 173).

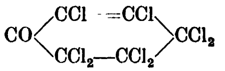
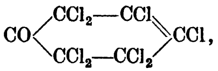
Halogen-substituted cyclic ketones of cyclohexenes are produced by the action of Cl_2 on phenols, anilines, hydroxy-benzoic acids, etc. They decompose easily (see vol. III) (*Zincke*, Ber. **23**, 3777; **25**, 2688; **27**, 547, 550, 560; Ann. **267**, 16; *Biltz*, Ber. **37**, 4003).

Heptachloro-cyclohexenones,

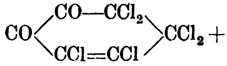
 and 

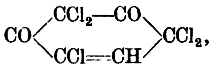
α-compound m.p. 98° and β-compound m.p. 80°, result from the action of chlorine upon-m-chloraniline.

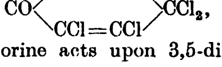
Octochloro-cyclohexenone,

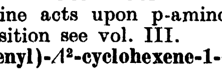
 or 

m.p. 103°, results from the action of chlorine upon pentachloro-phenol in AcOH solution, and from perchloro-m-hydroxy-benzoic acid. It can be reduced to pentachloro-phenol.

Hexachloro-1,2-cyclohexenedione,  $+2H_2O$, m.p. 93° decomp., is formed when chlorine acts upon pyrocatechol or o-aminophenol hydrochloride in AcOH. $SnCl_2$ reduces it to tetrachloro-o-benzoquinone (vol. III). Homologous 1,2-diketo chlorides have been obtained from o-diamino-methyl-benzenes.

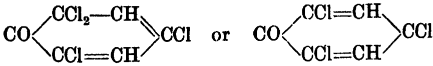
Pentachloro-1,3-cyclohexenedione,  m.p. 92°, b.p. 160°/25 mm., results from the action of chlorine on resorcinol in chloroform solution.

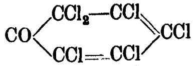
Hexachloro-1,3-cyclohexenedione,  m.p. 115°, b.p. 159°/14 mm., is produced when chlorine acts upon 3,5-dihydroxybenzoic acid in AcOH.

Hexachloro-1,4-cyclohexenedione,  m.p. 89°, b.p. 184°/45 mm., is formed when chlorine acts upon p-aminophenol hydrochloride in AcOH. For its decomposition see vol. III.

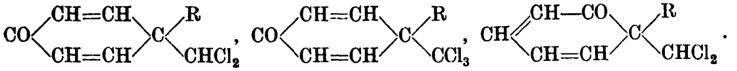
3-Methyl-5-(dimethyl-2′,6′-heptadienyl)-Δ^2-cyclohexene-1-one, b.p. 197–198°, is a ring ketone unsaturated in the ring as well as in the side chain. It is prepared by condensing citral (p. 204) with two molecules of ethyl aceto-acetate and treating the resulting citrylidene-bisaceto-acetic ester with alcoholic potash (*Knoevenagel*, J. pr. **97**, 331).

(c) Ring Ketones of Cyclohexadienes. — There are two possible cyclohexadienes, and from each a monoketone might be derived. Neither compound is known, since they are simply keto forms of ordinary phenol, but in **tetrachloro-cyclohexadienone,**



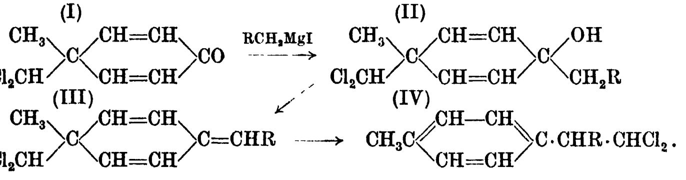
m.p. 122°, and in **hexachloro-cyclohexadienone,** , m.p. 106°, we have chloro derivatives of one or of both cyclohexadienones. The first compound is formed from trichloro-phenol and chlorine, and the second most conveniently by heating α-heptachloro-cyclohexenone (see above) (*Zincke*, Ber. **27**, 546), and also by treating phenol, anisole or pentachloro-aniline with chlorine (*Barral*, Bull. **11** (1895), 557).

Among the ring ketones of the dihydrobenzenes we must also include a series of substances obtained as by-products in the action of chloroform and alkali, or of carbon tetrachloride and aluminium chloride upon o- and p-alkylated phenols, e.g.:

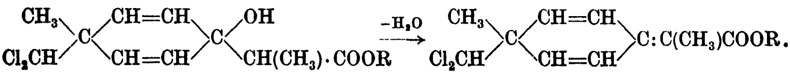


These compounds, which are reconverted by reduction with zinc dust and glacial acetic acid into the original phenols with liberation of CH_2Cl_2 or $CHCl_3$, react as ketones with phenylhydrazine, hydroxylamine, and semi-carbazide (*Auwers*, Ber. **36**, 1861), and are insoluble in alkalies (*Lindemann*, Ann. **431**, 270). They are only formed in aqueous alkaline solution and not from the dry alkali phenates. It is supposed that phenol and $CHCl_3$ form a short-lived addition product which loses HCl and gives $Ar \cdot OCHCl_2$.

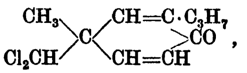
These ketones react with alkyl magnesium compounds to give compounds which are interesting because of the further changes which they undergo. The ketones (I) derived from *p*-alkyl-phenols yield normal tertiary alcohols (II) which split off water easily and give unstable alkylidene-dihydro-benzenes (III) or "semi-benzenes" (p. 97); the latter change into true benzene derivatives (IV) with migration of the $CHCl_2$ group, the change taking place in some cases at ordinary temperature and in others on heating (*Auwers*, Ann. **352**, 219; Ber. **55**, 2167):



With zinc and ethyl α-bromo-propionate the ketones (I) give esters of hydroxy-acids, which lose water under the action of formic acid and give *semibenzene-carboxylic esters*:

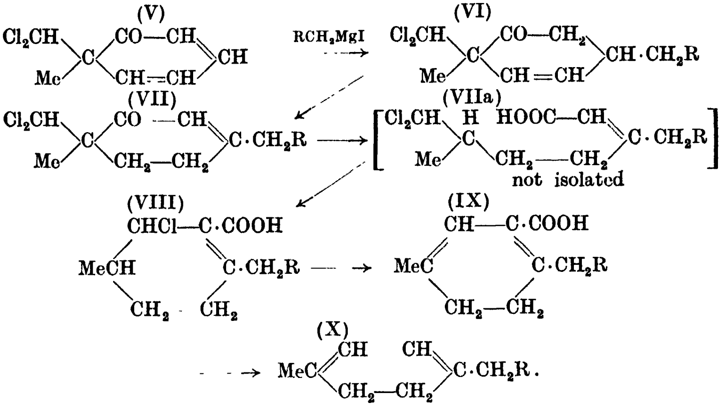


The free acids are unstable and change readily into true aromatic acids. When an isopropyl group is introduced into ketone (I), a hydroaromatic ketone

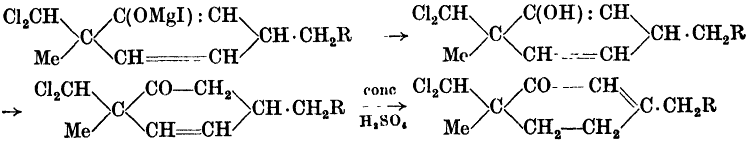


is formed in addition to the tertiary alcohol (II) (*Auwers*, Ber. **49**, 2396; Ann. **425**, 280).

The ketones derived from the o-alkyl-phenols (V) behave differently. The alkyl magnesium compound adds on to the carbon double link and forms higher homologous β,γ-unsaturated ketones (VI), which by the action of conc. sulphuric acid are converted into the isomeric α,β-unsaturated ketones (VII) with migration of the double bond. When the latter are heated with alcoholic potash, water adds on and the ring opens between the CO-group and the quaternary C-atom; the ring closes again with loss of HCl between the chlorinated C-atom and that which carries the newly-formed COOH-group (VIII), and finally p-dialkyl-dihydrobenzoic acids (IX) and 1,4-dialkyl-cyclohexadienes (X) are obtained (*Auwers*, Ber. 48, 1357, 1371):



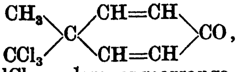
According to *Auwers* (Ber. 49, 2389) $IMgCH_2R$ adds on in the 1,4-position with subsequent ketonisation and rearrangement:



KOH then reacts as above. — By using isopropyl-MgI *Auwers* succeeded in synthesising α-terpinene (Ber. 48, 1358; cf. p. 210).

4-Methyl-4-dichloromethyl-cyclohexadienone (see above formula I), m.p. 55°, changes into trichloro-o-xylene $Cl[5]C_6H_3[1]Me[2]CHCl_2$ under the action of PCl_5, with intermediate formation of an unstable tetrachloride and migration of the Me-group (*Driver*, Am. 46, 2090). It combines with MeMgI to give **1,4-dimethyl-4-dichloromethyl-cyclohexadienol** (formula II, R=H). m.p. 96°, which decomposes easily into water and **1-methylene-4-methyl-4-dichloromethyl-cyclohexadiene** (III), a yellowish oil. On heating, the latter rearranges into 1-methyl-4(-β,β)-dichloroethyl-benzene (IV), while conc. sulphuric acid converts it into m-xylyl aldehyde, with migration of the Me-group.

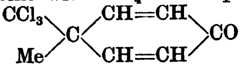
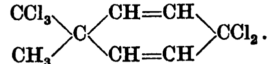
4-Methyl-4-trichloromethyl-cyclohexadienone,

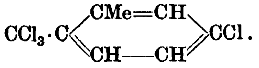


m.p. 105°, *oxime* m.p. 134°, from p-cresol, CCl_4 and $AlCl_3$, undergoes rearrangements which are similar to those of the corresponding dichloro compound (*Zincke*, Ber. 41, 897).

2-Methyl-2-dichloromethyl-cyclohexadienone, (V), m.p. 33°, b.p. 113°/9 mm., gives with MeMgI: **2,5-dimethyl-dichloromethyl-Δ^3-cyclohexenone,** *dichloro-*

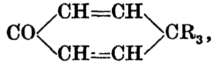
β,γ-pulenenone (VI), b.p. 124°/15 mm., which is converted by H_2SO_4 into the isomeric **2,5-dimethyl-2-dichloromethyl-Δ^5-cyclohexenone,** *dichloro-α,β-pulenenone* (VII), m.p. 41°, b.p. 151°/15 mm; the latter, with alcoholic potash, gives $\Delta^{1,3}$-dihydro-p-xylene (X), and by reduction with Na + EtOH: 3,6,6-trimethyl-cyclohexanol or *pulenol.*

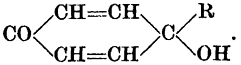
Some phenols, e.g. p-cresol, combine with CCl_4 in the presence of $AlCl_3$ to give trichloro-ketones, such as  which with *Grignard* compounds yield tertiary carbinols (p. 110). The latter lose water even at 35°, with formation of trichloro-semibenzenes (p. 97), which change into true benzene derivatives when heated with water. With PCl_3 these ketones give chlorides such as  These rearrange to chlorinated benzene homologues, with migration of methyl:



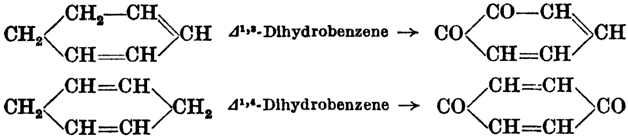
Zinc and ethyl bromo-acetate convert the ketones into hydroxy esters, which give with formic acid esters of *semibenzene-carboxylic acids* (p. 118) (*Auwers,* Ber. **55,** 2167).

The *methylene-quinones* and *quinols,* discussed later in connection with phenol alcohols (vol. III), are also monoketones derived from $\Delta^{1,4}$-dihydrobenzene:





Similarly, each of the two dihydrobenzenes is related to a diketone:



$\Delta^{1,3}$-Dihydrobenzene →

o-Benzoquinone, o-diketo-dihydrobenzene

$\Delta^{1,4}$-Dihydrobenzene →

p-Benzoquinone, p-diketo-dihydrobenzene

These compounds are also discussed in the aromatic section together with the phenols to which they are related.

4. EXOCYCLIC HYDROAROMATIC ALCOHOLS

Alcohols of this type have been obtained: (1) from saturated and unsaturated ω-cyclohexyl-Mg-(alkyl)-halides with ethylene oxide, aldehydes and ketones; (2) by reducing cyclohexane-carboxylic esters or exocyclic hydroaromatic ketones or by their reactions with alkyl-Mg halides; (3) by oxidising alkylidene-cyclohexanes with dilute permanganate; (4) from aromatic alcohols and their derivatives by catalytic hydrogenation (*Skita,* Ber. **48,** 1691); (5) from cyclohexanol by heating with aliphatic alcohols and $ZnCl_2$; (6) by reducing cyclohexenyl-carboxylic esters with Na and EtOH (*Becherer,* Helv. **8,** 184); (7) from cyclohexyl-Mg halides with CH_2O (*Gilman,* Org. Syntheses I 182).

Cyclohexylcarbinol	$C_6H_{11}CH_2OH$	b.p. 181°
***d,l*-Cyclohexylmethylcarbinol**	$C_6H_{11}CH(OH)CH_3$	b.p. 190°
***d*-Cyclohexylmethylcarbinol**		b.p. 82–83°/12 mm.
2-Methylcyclohexylcarbinol	$CH_3C_6H_{10}CH_2OH$	b.p. 115–117°/22 mm.
3-Methylcyclohexylcarbinol		b.p. 116–117°/23 mm.
4-Methylcyclohexylcarbinol		b.p. 106–107°/12 mm.
Cyclohexyldimethylcarbinol	$C_6H_{11}C(OH)(CH_3)_2$	b.p. 96°/20 mm.
***β*-Cyclohexylethylalcohol**	$C_6H_{11}CH_2CH_2OH$	b.p. 97–99°/15 mm.

β-Cyclohexylpropylalcohol $C_6H_{11}CH(CH_3)CH_2OH$ .. b.p.222–224°
γ-Cyclohexylpropylalcohol $C_6H_{11}CH_2.CH_2.CH_2OH$ .. b.p. 104–105°/12 mm.
α-Cyclohexylisopropylalcohol $C_6H_{11}CH_2CH(OH)CH_3$ b.p. 96–97°/27 mm.
1-Cyclohexyl-2-butanol $C_6H_{11}CH_2CH(OH)CH_2CH_3$ .. b.p. 126–127°/31 mm.
Alcohols $C_6H_{11}(CH_2)_nOH$ ($n = 1$ to 6), see *Hiers* and *Adams*, Am. **48**, 2383.

Cyclohexylcarbinol, *hexahydro-benzyl alcohol*, is obtained from hexahydrobenzoic ester with Na + EtOH (*Bouveault*, C. r. **137**, 60) or from cyclohexyl-MgBr with HCHO (*Favorsky*, Ber. **40**, 4863). It can be converted into the chloride, the aldehyde and the acid by the usual methods. *Chloride* b.p. 67–68°/20 mm.; *iodide* b.p. 103°/30 mm.

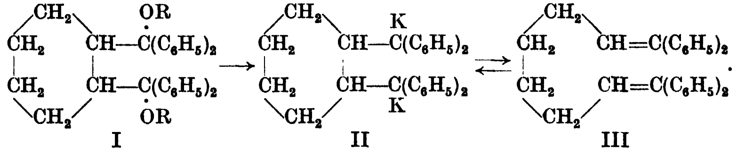
β-Cyclohexyl-ethyl alcohol, *β-hexahydrophenyl-ethyl alcohol*, is obtained from cyclohexylmethyl-MgI and trihydroxy-methylene (*Zelinsky*, Ber. **41**, 2628), and, in small quantities, in the reduction of ethyl phenylacetate by *Bouveault*'s and *Blanc*'s method. It smells feebly of peppermint, and not of roses like β-phenylethyl alcohol (*Darzens*, C. r. **189**, 852; *Sabetay*, Bull. **45** (1929), 482). **γ-Cyclohexylpropyl alcohol** has been obtained by complete hydrogenation of cinnamic aldehyde (*Skita*, Ber. **48**, 1692).

ω-Substituted cyclohexyl-alkyl bromides of the general formula $C_6H_{11}(CH_2)_nBr$, where $n = 1$ to 6, can be obtained from the alcohols with PBr_3 or with HBr + H_2SO_4 (*Hiers, Adams*, Am. **48**, 2385).

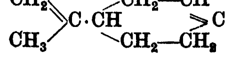
1-Methyl-cyclohexane-1,7-diol, $C_6H_{10}(OH)\cdot CH_2OH$, m.p. 77°, is formed in the oxidation of methylene-cyclohexane with $KMnO_4$, and from cyclohexene and trihydroxy-methylene with acetic and sulphuric acids (*Matti*, Bull. **51** (1932), 974). With acids it gives hexahydro-benzaldehyde (*Wallach*, Ann. **347**, 331).

1-Isopropyl-cyclohexane-1,7-diol $C_6H_{10}(OH)\cdot C(OH)Me_2$, m.p. 83°, from 1,1-cyclohexanol carboxylic ester with MeMgI, undergoes the pinacolin transformation when heated with dilute H_2SO_4 and gives 1-methyl-1-acetyl-cyclohexane (*Tarbouriech*, C. r. **150**, 1606).

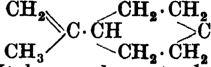
1,2-Bis-(diphenyl-hydroxymethyl)-cyclohexane, $C_{32}H_{32}O_2$, (formula I, R = H), cis m.p. 204–206° (*dimethyl ether* m.p. 170–172°); trans m.p. 185–185·5° (*dimethyl ether* m.p. 173–175°). Both are formed by the action of a solution of phenyl-lithium, made from bromobenzene and Li in Et_2O, upon cis or trans hexahydro-phthalic ester in abs. Et_2O under N_2. HCl + MeOH or boiling acetic acid convert them into the corresponding *glycol anhydrides* $C_{32}H_{30}O$, cis m.p. 199°, trans m.p. 221·5°. The diastereomeric *glycol-dimethyl-ethers* (formula (I), R = Me) are converted into red *organo-metallic compounds* (II) when shaken with a K-Na alloy under N_2. These are decomposed in alcohol to give the dibenzhydryl-cyclohexanes (cis and trans) (p. 91), which proves their constitution. When the metal atoms are removed by means of tetramethyl-ethylene-dibromide, the ring opens and 1,1,8,8-tetraphenyl-octadiene-1,7 $C_{32}H_{30}$ (III), m.p. 91–92°, is formed. The action of metals like K or Li upon this hydrocarbon partly regenerates the ring (II), and partly reduces it to *1,1,8,8-tetraphenyl-octane* $C_{32}H_{34}$, m.p. 120–121·5° (*Wittig*, Ber. **67**, 667):


I II III

Ring-unsaturated exocyclic alcohols have been found in several essential oils, e.g. a **dihydro-cuminalcohol,** *perillalcohol* $C_9H_{13}CH_2OH$ b.p. 119–121°/11 mm. in various oils such as those from gingergrass, *Cymbopogon martini* var. *sofia*, and from spearmint, *Mentha crispa*. Artificially, an alcohol of the formula


$$\overset{CH_2}{\underset{CH_3}{}}{>}C\cdot CH{<}\overset{CH_2-CH}{\underset{CH_2-CH_2}{}}{>}C\cdot CH_2OH$$

, has been made by reducing perillaldehyde (p. 229) with zinc dust and acetic acid. The same alcohol is formed when β-phellandrene glycol (p. 212) is heated with dilute H_2SO_4. Its chloride is reduced to *limonene* (p. 208) by Na+EtOH. By reducing the methyl ester of the corresponding perillic acid, or from dihydro-perillamine with $AgNO_3$, *dihydroperillalcohol*, $\begin{matrix}CH_2\\CH_3\end{matrix}\!\!>C\cdot CH\begin{matrix}CH_2\cdot CH_2\\CH_2\cdot CH_2\end{matrix}\!\!>CH\cdot CH_2OH$, b.p. 109–113°/13 mm., can be obtained. It has a pleasant odour of roses (*Semmler*, Ber. **44**, 460; *Williams*, C. 1930 I 2087.



For **1-methylol-2,6,6-trimethyl-Δ^2-(Δ^1-)-cyclohexene,** α- and *β-cyclogeraniol*, $C_{10}H_{18}O$, see Terpenes, p. 203.

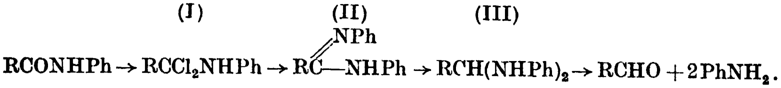
Vitamin A, which is discussed among the Natural Substances p. 562, also belongs to the exocyclic hydroaromatic alcohols.

Exocyclic Hydroaromatic Amines.—Cyclohexyl methylamine, *hexahydro-benzylamine*, $C_6H_{11}\cdot CH_2NH_2$, b.p. 163°, *benzoyl* compound m.p. 108°, is obtained from cyclohexyl-acetamide with KOBr, and from hexahydrobenzonitrile by reduction. With nitrous acid it partly undergoes ring enlargement and is transformed into cycloheptyl alcohol (p. 71) (*Wallach*, Ann. **353**, 298, 326; **414**, 229).

β-Cyclohexyl-ethylamine, $C_6H_{11}\cdot CH_2\cdot CH_2NH_2$, b.p. 188–189°, is obtained by reducing cyclohexyl-acetonitrile (*Wallach*, Ann. **353**, 297; *Waser*, Helv. **7**, 756).

5. HYDROAROMATIC ALDEHYDES

Hydroaromatic aldehydes can, for the most part, be prepared by the general methods for obtaining aldehydes, but it should be noticed that distillation of the calcium salts of the hydroaromatic carboxylic acids with calcium formate only gives poor yields of the aldehydes and is usually accompanied by rearrangements (see *Franke*, Mo. **46**, 61). On the other hand, the aldehydes can be prepared from the hydroaromatic acids by the following steps: conversion of the acid anilides into the anilide chloride (I) and the diphenyl-amidine (II), reduction of the latter with Na and EtOH and hydrolysis of the resulting alkylidene-dianilines (III) with dilute sulphuric acid (*Merling*, Ber. 41, 2064):



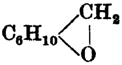
$$RCONHPh \rightarrow \overset{(I)}{RCCl_2NHPh} \rightarrow \overset{(II)}{R\overset{NPh}{\overset{/\!/}{C}}\!-\!NHPh} \rightarrow \overset{(III)}{RCH(NHPh)_2} \rightarrow RCHO + 2PhNH_2.$$

A number of aldehydes belonging to this group have become available through the *Diels-Alder* diene synthesis (p. 86). Several occur in essential oils.

(Alkyl-) *Cyclohexylidene aldehydes* of the general formula

$$R\cdot C_5H_9{>}C{:}CH\cdot CHO$$

are prepared by condensing (alkyl-) cyclanones and acetylene by means of $NaNH_2$, and treating the ethinyl alcohols so formed (p. 101) with formic acid (*Rupe*, Helv. **11**, 454).

Cyclohexane aldehyde, *hexahydro-benzaldehyde*, $C_6H_{11}\cdot CHO$, b.p. 162°, has been found in heavy acetone oil (*Pringsheim*, Angew. **40**, 1392) and is prepared (1) from the Ca-salt of cyclohexane carboxylic acid by distillation with Ca formate, (2) from cyclohexyl carbinol (p. 121) by oxidation with chromic acid or by catalytic dehydrogenation (*Adkins*, Am. **55**, 2992), (3) by reducing Δ^3-tetrahydro-benzaldehyde, (4) from the glycol of methylenecyclohexane (p. 121) with dilute H_2SO_4 (*Wallach*, Ann. **347**, 331), (5) from synthetic cyclohexyl-glycidic ester, which is readily accessible (p. 137), by hydrolysing and then removing CO_2 (*Darzens*, C. r. **142**, 714), (6) from cyclohexyl-Mg-bromide and ethyl orthoformate (*Wood*, J. Soc. Chem. Ind. **42**, T 429), (7) by hydrogenating benzylaniline under pressure and then oxidising and decomposing with HCl (*Skita*, Ber. **48**, 1689), (8) from cyclohexanone and CH_2N_2, by isomerisation of the hypothetical intermediate  $C_6H_{10}\langle{}^{CH_2}_{O}\rangle$, in presence of piperidine (*Mosettig*, Am. **52**, 3456). The compound smells of oil of bitter almonds and valeraldehyde, and readily polymerises to a dimeric form called *meta-hexahydrobenzaldehyde*, $(C_7H_{12}O)_2$, m.p. 202°; *oxime*, m.p. 91°; *semicarbazone*, m.p. 174° (*Zelinsky*, Ber. **40**, 3050). It loses CO in sunlight and gives cyclohexane. With formaldehyde and alcoholic potash it yields *1,1-dimethylol-cyclohexane*, m.p. 95° (*Franke*, Mo. **46**, 70); it condenses with acetophenone to hexahydrobenzylidene-acetophenone, m.p. 58–59° (*Frézouls*, C. r. **154**, 1707). For its condensation with malonic acid see *Sircar*, J. **1928**, 54.

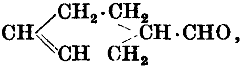
A number of homologous aldehydes, some of which occur in stereoisomeric forms, have been prepared by methods (2) and (3): **cis-2-methyl-hexahydrobenzaldehyde,** *hexahydro-o-tolylaldehyde*, $MeC_6H_{10}\cdot CHO$, b.p. 70°/24 mm., trans b.p. 72°/24 mm.; **3-methyl-hexahydrobenzaldehyde,** b.p. 95°/35 mm.; configuration unknown; **4-hexahydrotolylaldehyde,** trans b.p. 75–76°/24 mm. (*Skita*, Ann. **431**, 16). The 3-compound is also obtained from 1,3-methylcyclohexyl-MgBr and ethyl orthoformate. **2,6,6-Trimethyl-hexahydrobenzaldehyde,** b.p. 59°/10 mm., is prepared by reducing β-cyclocitral (p. 205) with H_2 and colloidal Pd (*Skita*, Ber. **42**, 1635).

Cyclohexyl-acetaldehyde, *hexahydro-phenylacetaldehyde*, b.p. 68°/12 mm., *semicarbazone* m.p. 153°, from cyclohexylidene-acetaldehyde (see above) by reduction, either with Zn and acetic acid or catalytically (*Rupe*, Helv. **11**, 456). **β-Cyclohexyl-propionaldehyde,** *β-hexahydro-phenylpropionaldehyde*, b.p. 87–88°/15 mm., *semicarbazone* m.p. 133°, from the acetal of (hydro-) cinnamic aldehyde or from the alcohol with chromic acid (*Sigmund*, Mo. **52**, 187; *Skita*, Ber. **48**, 1693).

Aldehydes of the general formula $C_6H_{11}\cdot CH_2\cdot CH_2\cdot CHR\cdot CHO$ have a characteristic odour of some value in perfumery and are prepared from exocyclic ketones containing one carbon less (with or without alkyl groups on the ring), by means of the glycidic esters (p. 137) (Germ. Pat. 501,627).

Δ^1-Cyclohexene-aldehyde, Δ^1-tetrahydrobenzaldehyde, $C_6H_9\cdot CHO$, an oil smelling very like benzaldehyde, is formed by loss of HCl and hydrolysis from the nitrosochloride of methylene-cyclohexane by means of NaAc and AcOH; *oxime*, m.p. 58°, *semicarbazone*, m.p. 212°. The corresponding derivatives of methyl-cyclohexane can be prepared similarly (*Wallach*, Ann. **359**, 292).

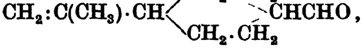
Δ^3-Cyclohexene-aldehyde, *Δ^3-tetrahydrobenzaldehyde*,



$$CH\langle{}^{CH_2\cdot CH_2}_{CH\quad CH_2}\rangle CH\cdot CHO,$$

b.p. 51–52°/13 mm., *semicarbazone* m.p. 153·5–154·5°, is prepared from Δ^3-cyclohexenyl-MgBr and ethyl orthoformate (*Sobecki*, Ber. **43**, 1040) or from butadiene and acrolein; isoprene or homologous butadienes and acrolein or crotonaldehyde give alkyl derivatives of this aldehyde which smell of leaves (*Diels*, *Alder*, Ann. **460**, 121; **470**, 85). All these aldehydes give the corresponding hexahydro-benzaldehydes and hexahydro-benzylalcohols on catalytic reduction, and secondary alcohols with *Grignard* reagents. Cf. French Pat. 672,025.

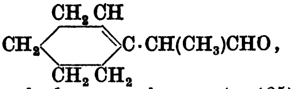
4-Isopropenyl-hexahydrobenzaldehyde, *dihydroperillaldehyde*,



$$CH_2{:}C(CH_3)\cdot CH\langle{}^{CH_2\cdot CH_2}_{CH_2\cdot CH_2}\rangle CHCHO,$$

b.p. 93–96°/12 mm., *semicarbazone* m.p. 123–124°, from the corresponding alcohol (p. 122).

The isomeric aldehydes $C_{10}H_{16}O$: Δ^1 and **Δ^2-tetrahydro-cuminaldehyde** (*phellandral*, *cryptal*) and the four *cyclocitrals* are discussed with the Terpenes p. 203.

Δ^1-Tetrahydrohydratropic aldehyde,  $CH_2\langle{}^{CH_2\,CH}_{CH_2\,CH_2}\rangle C\cdot CH(CH_3)CHO$, b.p. 90–93°/15 mm., is obtained from Δ^1-tetrahydro-acetophenone (p. 125) with ethyl chloro-acetate, a glycidic ester being first formed (*Darzens*, C. r. **151**, 758).

$\Delta^{1,3}$-Cyclohexadiene aldehyde, *$\Delta^{1,3}$-dihydro-benzaldehyde*, $C_6H_7\cdot CHO$, b.p. 122°/120 mm., is produced from anhydro-ecgonine dibromide (vol. IV) with sodium carbonate, and gives dihydrobenzoic acid (p. 133) when carefully oxidised with Ag_2O (*Willstätter*, Ber. **31**, 1545).

2,6,6-Trimethyl-$\Delta^{1,3}$-dihydrobenzaldehyde, *safranal*, $C_{10}H_{14}O$, b.p. 93°/14 mm., occurs as a glucoside *picrocrocin* (p. 484) in *Crocus sativa* (*Kuhn*, Ber. **67**, 354). For its preparation from β-cyclocitral and SeO_2 see id. C. 1937 I 2040.

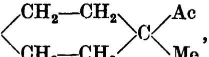
$\Delta^{1,5}$-Dihydrocuminaldehyde, $C_3H_7\cdot C_6H_6\cdot CHO$, *oxime*, m.p. 43°, *semicarbazone*, m.p. 202°, is formed by reduction of nitro-β-phellandrene (p. 213) (*Wallach*, Ann. **340**, 3), or from β-phellandrene nitrosochloride with acetic acid (*Francesconi*, Gazz. **46**, I 119). The isomeric **$\Delta^{1,8(9)}$-dihydrocuminaldehyde,** *perillaldehyde*, is described with the Terpenes p. 229.

6. EXOCYCLIC HYDROAROMATIC KETONES

The important violet perfumes, *irone* and the *ionones*, belong to this class.

Preparation: (1) Oxidation of exocyclic secondary alcohols; (2) from α-alkyl-cyclohexyl-glycidic esters (p. 137) by hydrolysis and loss of CO_2; (3) by condensation of cyclohexanones with ethyl acetate or aceto-acetate, acetone, or its homologues, by means of sodium; (4) ring-unsaturated ketones are obtained from the nitrosochlorides of alkylidene-cyclohexanes with zinc dust and acetic acid, or by removal of HCl and hydrolysis of the resulting oximes (*Wallach*, Ann. **360**, 39; **389**, 188).

Acetyl-cyclohexane, *hexahydro-acetophenone*, $C_6H_{11}Ac$, b.p. 68°/12 mm., is prepared by methods (1), (2) and (4), from cyclohexene and acetyl chloride with $AlCl_3$ (*Nenitzescu*, Ann. **510**, 276), and from α-acetyl-cyclohexane-carboxylic ester (p. 20 and 138); *semicarbazone*, m.p. 175° (*Zelinsky*, Ann. **508**, 115). For the Beckmann rearrangement of the oxime see *Manta*, Bull. **51** (1932), 1005.

1,1-Methyl-acetyl-cyclohexane,  $CH_2\langle{}^{CH_2-CH_2}_{CH_2-CH_2}\rangle C\langle{}^{Ac}_{Me}$, b.p. 83°/18 mm., is obtained from isopropyl-cyclohexane-1,7-diol (p. 121) with dilute H_2SO_4 (*Tarbouriech*, C. r. **150**, 1606). **Methyl-hexahydro-acetophenones,** *hexahydro-acetyl-toluenes* 2-, 3- and 4-, b.p. 75–80°/18 mm., b.p. 76–77°/13 mm. and b.p. 74°/12 mm., are prepared by method (2) (*Darzens*, C. r. **144**, 1123; *van Woerden*, Rec. **45**, 124).

Hexahydro-propiophenone, $C_6H_{11}\cdot COEt$, b.p. 196°, has been obtained by oxidation of cyclohexyl-ethyl-carbinol, and by the action of zinc ethyl upon hexahydro-benzoyl chloride. — For cyclohexyl ketones with higher alkyl groups see *Nenitzescu*, Ber. **69**, 1820.

Cyclohexylacetone, $C_6H_{11}\cdot CH_2\cdot CO\cdot CH_3$, b.p. 196°, from cyclohexyl-aceto-acetic ester (*Hell*, Ber. **42**, 2230).

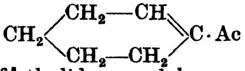
1-Hydroxy-4-methyl-hexahydro-acetophenone, m.p. 21–22°, is an intermediate in method (4). It gives Δ^1-tetrahydro-4-methyl-acetophenone (see below) with dilute H_2SO_4.

2-Acetyl-cyclohexanone, $C_6H_9O\cdot Ac$, b.p. 111°/18 mm., obtained by method (3), is hydrolysed by alkalies to acetyl-caproic acid. It can be alkylated by means of sodium and alkyl iodide, and reacts with amidines to form tetrahydro-quinazolines (vol. IV). **3,6-Methyl-acetyl-cyclohexanone,** $C_6H_8O[3,6](Me)(Ac)$, b.p. 122°/14 mm. (*Léser*, Bull. C. r. **141**, 1032; Bull. **25**, (1901), 196). — For isomeric Me-acetyl-cyclanones see *Sen*, J. Ind. ch. Soc. **4**, 51.

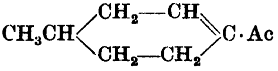
2-Propionyl-cyclohexanone, $C_6H_9O\cdot COEt$, b.p. 123°/21 mm., is formed by nuclear synthesis from ζ-keto-nonylic ester and NaOEt (*Blaise*, C. r. **148**, 1401).

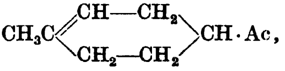
Acetyl-1,3,5-cyclohexane-trione, m.p. 218°, from phloroglucinol and acetonitrile by means of HCl, shows the reactions of both the ketonic and enolic forms. Mono-, di- and tri-acetylated 1,3,5-cyclohexane-triones are obtained by rearrangement of the corresponding acetates of phloroglucinol by means of $ZnCl_2$ (*Heller*, Ber. **45**, 418; **48**, 1286).

1-Phenyl-2-acetyl-cyclohexane, b.p. 161–164°/11 mm., from cyclohexene, acetyl chloride and benzene with $AlCl_3$ (*Nenitzescu*, Ann. **519**, 265).

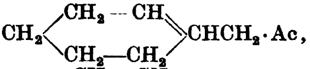
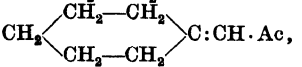
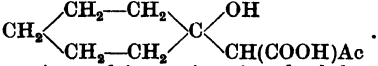
Δ^1-Tetrahydro-acetophenone,  $CH_2\Big\langle\begin{matrix}CH_2-CH\\CH_2-CH_2\end{matrix}\Big\rangle C\cdot Ac$, b.p. 201°, is obtained from the nitrosochloride of ethylidene-cyclohexane (p. 95), and by the action of acetyl chloride and $AlCl_3$ or, preferably, $SnCl_4$ upon cyclohexene or cyclohexane at 18–35° (*Darzens*, C. r. **150**, 707; *Wieland*, Ber. **55**, 2246; *Zelinsky*, Ann. **508**, 115). It is also obtained from cyclohexanone with $AlCl_3+CH_3COCl$ and from cyclohexene and acetic anhydride in the presence of a little conc. H_2SO_4 and sulphacetic acid (*Ebel*, Helv. **10**, 677). *Oxime* m.p. 99°. *Semicarbazone* m.p. 220–221° dec.

4-Methyl-Δ^1-tetrahydro-acetophenone, *Δ^3-tetrahydro-p-acetyl-toluene* (I), b.p. 213°, from 4-methyl-ethylidene-cyclohexane with NOCl. **4-Methyl-Δ^3-tetrahydro-acetophenone,** *Δ^1-tetrahydro-p-acetyl-toluene,* (II), b.p. 205–206°,

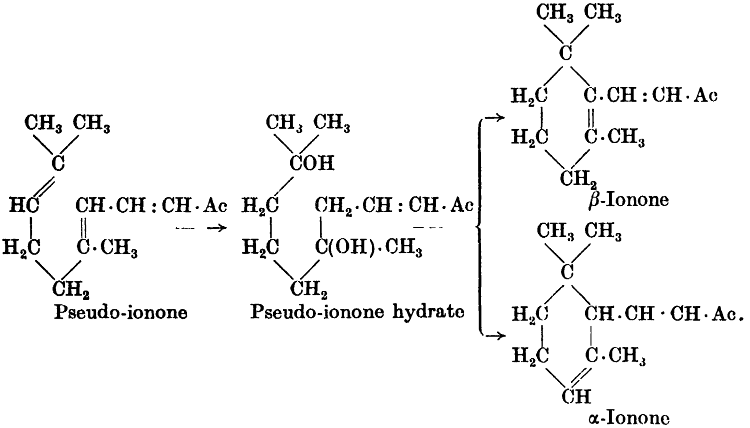
(I) 
$CH_3CH\Big\langle\begin{matrix}CH_2-CH\\CH_2-CH_2\end{matrix}\Big\rangle C\cdot Ac$

 (II)
$CH_3C\Big\langle\begin{matrix}CH-CH_2\\CH_2-CH_2\end{matrix}\Big\rangle CH\cdot Ac,$

probably occurs in cedar oil from the Himalaya and the Atlas (*Grimal*, C. r. **135**, 582; *Roberts*, J. **109**, 791). It is made artificially from β-terpineol (p. 224) with CrO_3, and is reduced by nascent hydrogen to the next lower homologue of α-terpineol. With MeMg-halide it gives *homo-α-terpineol.* Both ketones give p-methyl-hexahydro-acetophenone when hydrogenated by *Paal's* method (see above).

Δ^1-Cyclohexenyl-acetone,  $CH_2\Big\langle\begin{matrix}CH_2-CH\\CH_2-CH_2\end{matrix}\Big\rangle CHCH_2\cdot Ac$, b.p. 83°/12 mm., and **Cyclohexylidene-acetone,**  $CH_2\Big\langle\begin{matrix}CH_2-CH_2\\CH_2-CH_2\end{matrix}\Big\rangle C{:}CH\cdot Ac$, b.p. 95°/17 mm., have been obtained by *Dickins, Hugh* and *Kon* (J. **1928**, 1630) as follows: Cyclohexanone and ethyl Na-aceto-acetate combine to form the ester of the acid  $CH_2\Big\langle\begin{matrix}CH_2-CH_2\\CH_2-CH_2\end{matrix}\Big\rangle C\Big\langle\begin{matrix}OH\\CH(COOH)Ac\end{matrix}$. Heating the free acid in vacuo above its melting point gives both ketones. They are also obtained from cyclohexenyl- or cyclohexylidene-acetyl chloride by means of MeZnI. The former ketone has also been obtained by the distillation of cyclohexane-diacetic acid (*Kon*, J. **119**, 825). The *semicarbazone* of the former occurs in two forms, m.ps. 145° and 136°; that of the latter melts at 180°; the ketones can be regenerated from them (id. J. **1930**, 1616). **Cyclohexenyl- and cyclohexylidene-acetophenones** have been prepared by *Farrow* and *Kon*, J. **1926**, 2128.

α-Ionone (see below), b.p. 127°/12 mm., d_{20} 0·9301, and **β-ionone** (see below), b.p. 127°/10 mm., d_{20} 0·9442 (*Tiemann*, Ber. **26**, 2691; **31**, 808), when concentrated smell like cedarwood, but when highly diluted have an intense odour of violets very like that of irone, and they are therefore made on a large scale. Their occurrence in the vegetable kingdom has not been established with certainty, except that of β-ionone in the oil of *Boronia megastigma* (*Sabetay*, C. r. **189**, 808). They are prepared from the cyclocitrals (p. 205) and acetone by means of condensing agents, such as NaOEt, aqueous baryta, $NaNH_2$ etc., or from pseudo-ionone (below) with conc. sulphuric acid, or phosphoric acid, or by heating to 190° under pressure with aqueous salt solutions (Germ. Pat. 158,075). In the latter case a mixture of α- and β-ionones in varying proportion is formed; this can be explained by the successive addition and loss of water:


Pseudo-ionone

Pseudo-ionone hydrate

β-Ionone

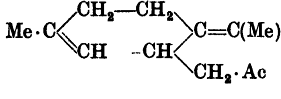
α-Ionone

The pseudo-ionone hydrate, shown as an intermediate product, has been isolated (Germ. Pat. 172,653). The constitution of the two ionones follows from their decomposition products: on oxidation α-ionone gives β,β-dimethyl-adipic acid and β-ionone α,α-dimethyl-adipic acid.

The two ionones can be separated through their bisulphite compounds which are readily formed when crude ionone is treated with sodium bisulphite and are hydrolysed by alkali. When treated with steam, the β-salt decomposes and the ketone distils over, while the α-salt remains unchanged. For the condensation of β-ionone with Zn and ethyl bromo-acetate see *Karrer*, Helv. **15**, 878.

When the ionones are reduced with H_2 and Pd, two different *dihydro-ionones* are formed, while exhaustive reduction results in only one *tetrahydro-ionone*. Thit shows that the exocyclic double bond is the first to be saturated. These dihydro-ionones are nearly odourless. A different ring-saturated dihydro-ionone of intense odour is obtained from dihydro-cyclocitral and acetone, which shows that the odour depends on the exocyclic double bond. When the reduction is carried out with Pt and acetic acid, the CO-group is reduced as well and tetrahydro-ionol is formed (*Skita*, Ber. **45**, 3312; **48**, 1495; *Ruzicka*, Helv. **2**, 352).

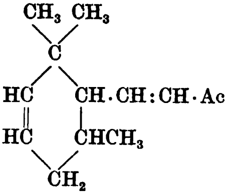
Isomeric ionones with a different grouping of the side chains, viz. **β-pseudo-ionone,** *a*- and **β-iso-ionones,** can be obtained from the different citrals with ethyl aceto-acetate. The esters which are the first products are hydrolysed and the acids are heated above their melting points. When the enol-acetate of ψ-ionone is boiled with KOH in EtOH, the ring closes and **iso-ψ-ionone,** *3-acetonyl-terpinolene*, a true terpene compound, is formed



$$\mathrm{Me{\cdot}C}\begin{matrix}\diagup CH_2{-}CH_2\diagdown \\ \diagdown CH\ \ {-}\underset{\diagdown CH_2\cdot Ac}{CH}\diagup\end{matrix}\mathrm{C{=}C(Me)_2}$$

(*Knoevenagel*, J. pr. **97**, 288; **102**, 305, table I).

An *isomeric ionone* (the so-called "irone" of *Tiemann*),



has been synthesised from the chlorohydrin of rhodinal (p. 204) by condensation with acetone; the resulting pseudo-ionone is cyclised to the hydrochloride of "irone", the phenylhydrazone of which yields the ketone by boiling with dilute sulphuric acid (*Verley*, Bull. **2** (1935), 1205).

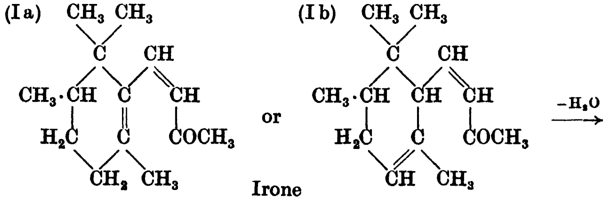
The ketones of the ionone group differ from those of the irone group, which are discussed below, not only in the fact that they contain a methyl group less, but also structurally, in the positions of the double bond in the ring, and stereochemically, in the arrangement of the substituents with respect to the ring. In the irone series the arrangement is trans, and in the ionones it is cis (*Ruzicka,* Helv. **2,** 352).

Homologous ionones are obtained from citral and homologues of acetone with ψ-ionones as intermediates. Besides the CO-group, both the CH_3- and the CH_2-group may take part in the reaction. Four methyl ionones have been obtained by *Koster* (J. pr. **143,** 249) from methyl ethyl ketone and α- and β-cyclocitral (p. 205).

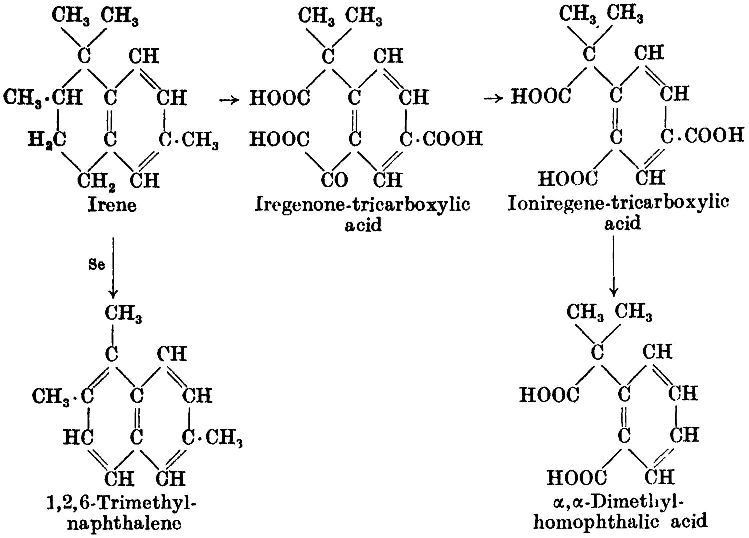
Karrer describes ketonic substances resembling ionone in odour, obtained from carotenes (p. 407) and vitamin A (p. 562) on oxidation with $KMnO_4$ (Helv. **12,** 1142; **13,** 1084). For partially hydrogenated products of vitamin A from β-ionone and tetrahydro-ionone see *Gould,* Am. **57,** 340.

Irone, $C_{14}H_{22}O$, b.p. 96–98°/0·4 mm., d_4^{17} 0·939, $[\alpha]_D$ +46° was first isolated by *Tiemann* and *Kruger* (Ber. **26,** 2675) from the essential oil of the orris root from *Iris florentina, Iris germanica* and *Iris pallida.* It seems to occur in wall-flower oil as well (*Kummert-E.,* Chem.-Ztg. **35,** 667). It has an intense odour of violets, especially when highly diluted. The formula given by the discoverers, $C_{13}H_{20}O$, was amended to $C_{14}H_{22}O$ by *Ruzicka* (Helv. **16,** 1143). While irone is a cyclohexane derivative, Ia or Ib, an isomeric cycloheptane form is not excluded, for β,β,γ-trimethyl-pimelic acid has been obtained by ozonising one particular irone preparation. The synthesis from Δ^3- and Δ^4-cyclocitrals and acetone, which *Merling* and *Welde* (Ann. **366,** 119) undertook on the strength of the formula $C_{13}H_{20}O$, really gives α-ionone, as *Ruzicka* has shown.

Irone thiosemicarbazone, made from orris oil of 1903, had the melting point 181°, but made from the oil of 1928 it melted at 121–122°. *p-Bromophenylhydrazone* m.p. 175°; *phenylsemicarbazone* m.p. 178–179°. From these derivatives unchanged irone is only regenerated by boiling with phthalic acid, since boiling with aqueous oxalic acid leads to an irone of different physical and chemical properties, $[\alpha]_D$ up to +96°, while the derivatives melt at ill-defined temperatures. Boiling with HI and P converts irone into irene (p. 174). Oxidation gives successively *dehydro-irene, iregenone-di-* and *-tri-carboxylic acids, ioniregene-tricarboxylic acid,* and finally α,α-dimethylhomophthalic acid:



Irone



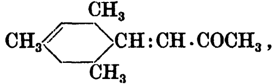
Irene

Iregenone-tricarboxylic acid

Ioniregene-tricarboxylic acid

1,2,6-Trimethylnaphthalene

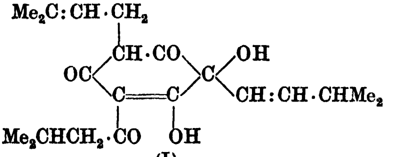
α,α-Dimethylhomophthalic acid

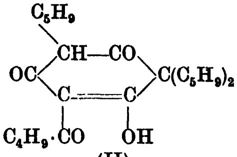
Numerous ring ketones of the irone type have been a prepared by *Diels* and *Alder*, who obtained Δ^3-tetrahydro-benzaldehydes by their diene-synthesis and condensed them with acetone etc. Thus 2,4,6-Me_3-tetrahydrobenzaldehyde and acetone give a ketone  $\mathrm{CH_3}\langle\overset{\mathrm{CH_3}}{\underset{\mathrm{CH_3}}{\bigcirc}}\rangle\mathrm{CH{:}CH{\cdot}COCH_3}$, b.p. 138–139°/20 mm. which has been given the name **"pseudo-irone"** in spite of its cyclic structure; on the basis of the formula for irone proposed by *Ruzicka*, it might be called *iso-apo-irone*. Its *p-bromo-phenylhydrazone* melts at 175°.

An *isomeric irone* has been obtained from 2,4,6,6-tetramethyl-Δ^4-tetrahydrobenzaldehyde (*Diels, Alder*, Ann. **470**, 96; French Pat. 672,025, 679,443).

The following isoamenyl-isovaleryl unsaturated cyclic hydroxy-triketones have been isolated from hop-resin:

Humulone (I), m.p. 65–66·5°, and **lupulone** (II), m.p. 90·5–92° (*Wieland*, Ber. **59**, 2352; cf. pp. 400, 401)


(I)


(II)

7. HYDROAROMATIC CARBOXYLIC ACIDS

A large number of hydroaromatic carboxylic, hydroxycarboxylic, keto- and di-carboxylic acids is known. *Quinic* and *shikimic* acids (p. 135) are among the hydroxycarboxylic acids, *succino-succinic*

acid is a keto-carboxylic acid (p. 146). Other keto-carboxylic esters are used as the starting material for the synthesis of simple hydroaromatic compounds (p. 83).

(A) Hydroaromatic Monocarboxylic Acids

A direct introduction of the carboxyl group into the nucleus of hydroaromatic substances can be brought about by the action of CO_2 upon the cyclohexyl-magnesium halides:

$$C_6H_{11}I \xrightarrow[CO_2]{Mg} C_6H_{11}CO_2MgI \xrightarrow{HCl} C_6H_{11}CO_2H.$$

On the other hand, the reaction of cyclohexyl halides with KCN or ethyl sodio-malonate is of little value, since in almost all cases the only product is cyclohexene, formed by elimination of hydrogen halide (p. 92).

(a_1) Cyclohexane-carboxylic Acids, Hexahydro-benzoic Acids have been obtained by the reduction of benzoic acid and its homologues with metallic sodium in boiling amyl or capryl alcohols or by reducing sodium benzoate in aqueous solution with sodium in a stream of CO_2 (*Aschan*, Ber. **24**, 1865; *Markovnikov*, ib. **25**, 3355).

The term "naphthenic acids", which was formerly used for the hydroaromatic acids, has been shown by recent investigations to be misleading and should be avoided (*Aschan*, "Naphthenverbindungen", Berlin 1929, p. 4). A comparison of hexanaphthene carboxylic and hexahydro-benzoic acids shows the following differences:

		hexanaphthene carboxylic acid	hexahydrobenzoic acid
Free acid	b.p.	215–217°	232°
Methyl ester	„	165·5–167·5°	183°
Chloride	„	167–169°	179°
Amide	m.p.	123·5°	185°
Anilide	„	93–94°	131°

Further, no hexahydrogenated aromatic monocarboxylic acids have been found in the fractions of the methyl esters prepared from naphthenic acids, which boil in the region of 180°. The naphthenic acids do not decompose into H_2 and aromatic compounds on dehydrogenation like true cyclohexyl derivatives (*Zelinsky*, Ber. **57**, 42, 51). They cannot therefore be cyclohexane derivatives, but are derived from other cycloparaffins, mainly cyclopentane (l. c., p. 8; *v. Braun*, Ann. **490**, 105; this vol. p. 64).

Cyclohexane-monocarboxylic acids can be prepared by heating cyclohexane-1,1-dicarboxylic acids (p. 140) which can be obtained synthetically, just as malonic acids give the fatty acids.

The cyclohexane-carboxylic acids are weak acids; their dissociation constants have been measured by *Zelinsky*, C. 1909 I 531. The velocity of esterification has been investigated by *Bhide* and *Sudborough*, J. Ind. Inst. Sc. A 8 (1925), 89. Hot HI reduces them to hexahydro-aromatic hydrocarbons, so-called "*naphthenes*", with the same number of C-atoms in the molecule. A general review of the hydroaromatic acids is given by *Auwers*, Ber. **48**, 1377.

Hexahydrobenzoic acid, *Cyclohexane-carboxylic acid*, $C_6H_{11}\cdot CO_2H$, m.p. 31°, b.p. 232°, is formed in the reduction of benzoic acid, Δ^2-tetrahydrobenzoic acid (*Aschan*, Ann. **271**, 261), p-dimethylamino-benzoic acid (*Einhorn*, Ber. **27**, 2829), and cyclohexanol-1-carboxylic acid or its methyl ester (*Bucherer*, Ber. **27**, 1231). It is also obtained by heating cyclohexane-1,1-dicarboxylic acid, and by treating Cl-, Br- or I-cyclohexane with Mg and CO_2 (*Zelinsky*, Ber. **35**, 2688). *Calcium salt*, $(C_4H_{11}O_2)_2Ca + 5\,H_2O$. *Chloride* b.p. 179° (*Meyer*, Ber. **30**, 1941). *Methyl ester* b.p. 183°, *ethyl ester* b.p. 196°, *amide* m.p. 185°, *anhydride* b.p. 171°/14 mm. The *peroxide* $(C_6H_{11}COO)_2$ is an unstable oil, prepared from the anhydride by means of BaO_2 hydrate (*Fichter*, Helv. **15**, 1304). The *anilide* m.p. 131° is formed by the rearrangement of β-hexahydro-benzophenone oxime (p. 106; *Scharvin*, Ber. **30**, 2862). The *phenyl ester*, b.p. 163–164°/21 mm., rearranges when heated or treated with $ZnCl_2$ into *cyclohexyl-o-hydroxyphenyl ketone*, $C_6H_{11}\cdot CO\cdot C_6H_4OH$, m.p. 41–42° (*Skraup*, Ber. **60**, 1070).

1-Methylcyclohexane-1-carboxylic acid	m.p. 39°	b.p. 234°	(Ber. **40**, 2069)
trans-Hexahydro-o-toluic acid	m.p. 52°	b.p. 241–242°	(Ber. **41**, 2679)
cis-Hexahydro-o-toluic acid	liquid	b.p. 238,5-240°	(Ann. **431**, 18)
Hexahydro-m-toluic acid	liquid	b.p. 240°	
α-Hexahydro-p-toluic acid	m.p. 113°	b.p. 246°	(J. pr. **110**, 101)
β-Hexahydro-p-toluic acid	liquid		
2,4-Hexahydro-xylic acid	m.p. 77°	b.p. 156°/40 mm.	
3,4-Hexahydro-xylic acid	liquid	b.p. 251°	
2,6-Hexahydro-xylic acid	m.p. 72°	b.p. 251°	
3,5-Hexahydro-xylic acid	liquid	b.p. 139°/15 mm.	
Hexahydrocumic acid	m.p. 96°		

The acids are prepared partly by the reduction of the corresponding benzene-carboxylic acids, and partly by the action of Mg and CO_2 upon the halogen-substituted cyclohexanes. Hexahydro-o-toluic acid is formed from 2-methyl-cyclohexane-1,1-acetyl-carboxylic ester and -1,1-dicarboxylic ester. The liquid cis-acid has been obtained by reduction of its bromine substitution product. The liquid p-hexahydro-toluic acid has been obtained from tropilidene-carboxylic acid (*Markovnikov*, J. pr. **57**, 102; *Sernov*, Ber. **32**, 1167; *Noyes*, Am. Chem. J. **22**, 1).

Homologous hexahydro-benzoic acids with alkyls attached to the ring are obtained from Δ^3-tetrahydro-benzoic acids (see below), which have become easily accessible thanks to the diene synthesis (p. 86). *Hiers* and *Adams*, Am. **48**, 1089, describe six-ring homologues of dihydro-chaulmoogric and dihydro-hydnocarpic acids (p. 65).

1-Monobromo-hexahydrobenzoic acid, m.p. 63° and **1-monobromo-hexahydro-o-** and **-p-toluic acids,** m.p. 97° and 71° resp. are obtained by bromination of the chlorides of the corresponding hexahydro acids. Two isomeric monobromo derivatives of hexahydro-m-toluic acid are formed, m.ps. 118° and 142° (*Sernov*, l. c.). **2-Bromo-hexahydrobenzoic acid,** m.p. 108–109°, from Δ^1-tetrahydro-benzoic acid with HBr. **1,2-Dibromo-hexahydrobenzoic acid,** m.p. 142°, probably a mixture of two stereoisomers, is obtained from the same tetrahydro-acid with Br_2. **2,3-Dibromo-hexahydrobenzoic acid,** m.p. 166°, from the Δ^2-tetrahydro-acid with bromine, gives an α-bromolactone $C_7H_9O_2Br$, m.p. 67°, when boiled with aqueous Na_2CO_3 (*Aschan*, Ann. **271**, 231).

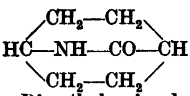
1-*Amino-hexahydrobenzoic acids* have been prepared by the action of NH_4CN upon cyclohexanones and hydrolysis of the resulting 1-amino-nitriles (*Skita*, Ber. **41**, 2925).

1-Amino-hexahydrobenzoic acid, $C_5H_{10}>C(NH_2)CO_2H$, m.p. 335°.

o-Amino-hexahydrobenzoic acid, *hexahydro-anthranilic acid,*

$$NH_2[2]C_6H_{10}\cdot CO_2H,$$

m.p. 274° decomp., is formed in the reduction of anthranilic acid with Na and amyl alcohol together with pimelic and hexahydrobenzoic acids (*Einhorn*, Ber. **27**, 2470; Ann. **295**, 187; *Orthner*, Biochem. Z. **262**, 461). **m-Amino-hexahydrobenzoic acid,** m.p. 269°, *ethyl ester* b.p. 123°/11 mm., results from reduction of m-amino-benzoic acid with Na and EtOH or amyl alcohol, together with several other substances (id. Ann. **319**, 324). **p-Amino-hexahydrobenzoic acid** sublimes at >330°; it is obtained by hydrogenating p-amino-benzoic acid; when heated it gives the lactam.

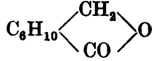


$HC\overset{CH_2-CH_2}{\underset{CH_2-CH_2}{-NH-CO-}}CH$, *iso-nortropinone* m.p. 191–192° (*Houben*, Ber. **49**, 2294).

p-Dimethylamino-hexahydrobenzoic acid, see *Einhorn*, Ber. **27**, 2831.

Other amino-cyclohexane carboxylic acids have been obtained by reducing oximes of cyclohexanone- and cyclohexenone-carboxylic esters with Na and EtOH (*Skita*, Ber. **40**, 4167).

trans-N-Diethyl-hexahydrobenzylamine-o-carboxylic acid, $Et_2NCH_2[2]C_6H_{10}COOH$, m.p. 101°, is obtained from diethyl-benzylamine-o-carboxylic acid by reduction with sodium and amyl alcohol. When heated with alkalies it is converted into the more strongly basic liquid cis-acid, which is easily decomposed into diethylamine and **2-methylol-hexahydrobenzoic acid,** $HOCH_2\cdot C_6H_{10}COOH$, m.p. 112°. This latter acid gives hexahydro-phthalide,



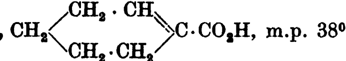
$C_6H_{10}\Big\langle\begin{matrix}CH_2\\CO\end{matrix}\Big\rangle O$

when heated. For **hexahydrobenzylamine-** and **diethyl-hexahydrobenzylamine-p-carboxylic acids,** see *Einhorn*, Ann. **300**, 161; **310**, 189.

Cyclohexyl-dithiocarboxylic acid, an evil-smelling, red-brown liquid which cannot be distilled, is obtained from cyclohexyl-MgBr and CS_2. The Hg-salt, m.p. 163°, is orange-red (*Bost*, *Williams*, Am. **52**, 4991).

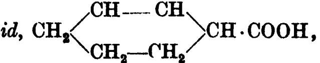
(a$_2$) Tetrahydrobenzoic Acids can be obtained from the monohydroxy- and monobromo-cyclohexane-carboxylic acids by splitting off H_2O or HBr, and also by the reduction of the benzoic acids and dihydrobenzoic acids (*Einhorn*, Ber. **26**, 457).

Δ^1-Tetrahydrobenzoic acid,



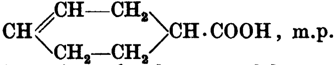
$CH_2\Big\langle\begin{matrix}CH_2\cdot CH\\CH_2\cdot CH_2\end{matrix}\Big\rangle C\cdot CO_2H$, m.p. 38°, b.p. 240°, is formed from 1-bromo-hexahydrobenzoic acid and $\Delta^{4,6}$-dihydrobenzoic acid, and from Δ^2-tetrahydrobenzoic acid by boiling with alcoholic potash (*Braren*, Ber. **33**, 3455) and also in the decomposition of phenyl-Δ^6-tetrahydrophthalide (*Berlingozzi*, Gazz. **57**, 255). *Amide* m.p. 127–128°.

Δ^2-Tetrahydrobenzoic acid, *benzoleinic acid,*

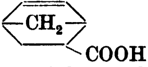


$CH_2\Big\langle\begin{matrix}CH-CH\\CH_2-CH_2\end{matrix}\Big\rangle CH\cdot COOH$, is a liquid boiling at 234° prepared from benzoic acid. *Amide*, m.p. 144° (*Boorman*, *Linstead*, J. **1935**, 258).

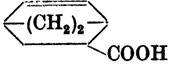
Δ^3-Tetrahydrobenzoic acid,



$CH\Big\langle\begin{matrix}CH-CH_2\\CH_2-CH_2\end{matrix}\Big\rangle CH\cdot COOH$, m.p. about 13°, b.p. 237°, can be obtained from 3- and 4-bromo-cyclohexane-carboxylic acid, and by the action of CO_2 and Mg upon Δ^3-bromo-cyclohexene (*Perkin*, J. **91**, 490; *Sobecki*, Ber. **48**, 1039). It is also formed by diene condensation of butadiene and acrylic acid. The same method has served for preparing homologues and also 1,4-endoalkylene-bridged derivatives of the types



and



(p. 186).

Of the **tetrahydro-toluic acids**[1] those listed below are known. Most of them have been obtained from the various methyl-bromo-cyclohexane carboxylic acids by removal of HBr by means of quinoline, pyridine etc., or more conveniently by the dehydration of cyclohexanol-carboxylic acids or the reduction of tetrahydrophthalides with HI and P. Most of this work has been carried out by *Perkin, jun.* and his collaborators (J. **87**, **89**, **91**, **97**, **99**, **108**).

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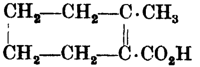
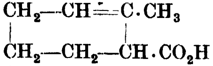
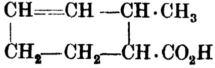
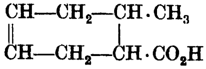
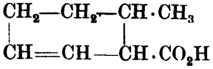
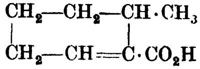
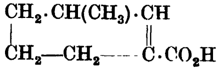
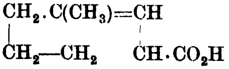
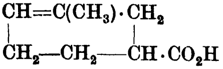
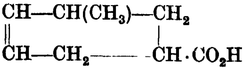
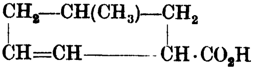
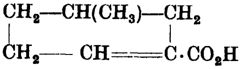
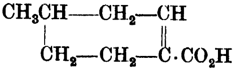
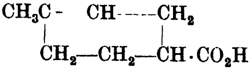
[1] The numbering Δ^1, Δ^2, etc. starts from the carboxylated C-atom and runs in the direction of the CH_3-group.

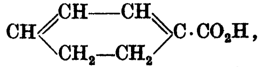
The Δ^1- and Δ^3-tetrahydro-p-toluic acids, and the Δ^2-, Δ^3-, Δ^4- and Δ^6-tetrahydro-m-toluic acids have been resolved into optically active forms by means of their salts with brucine and strychnine. *Sylvestrene* (p. 213) and *carvestrene* (p. 214) have been synthesised from Δ^3-tetrahydro-m-toluic acid, various *menthenols* (p. 225) from Δ^4- and Δ^5-tetrahydro-p-toluic acid, and *α-terpineol* (p. 223) and *dipentene* (p. 208) from Δ^3-tetrahydro-p-toluic acid (*Perkin, jun.*).

		M.p.		B.p.	[α]
		act.	d,l		
Δ^1-Tetrahydro-o-toluic acid	 $\begin{array}{l} CH_2-CH_2-C\cdot CH_3 \\ \mid \qquad\qquad\quad \| \\ CH_2-CH_2-C\cdot CO_2H \end{array}$		87–88°		
Δ^2-Tetrahydro-o-toluic acid	 $\begin{array}{l} CH_2-CH=C\cdot CH_3 \\ \mid \qquad\qquad\quad \mid \\ CH_2-CH_2-CH\cdot CO_2H \end{array}$			140–142°/ 20 mm.	
Δ^3-Tetrahydro-o-toluic acid	 $\begin{array}{l} CH=CH-CH\cdot CH_3 \\ \mid \qquad\qquad\quad \mid \\ CH_2-CH_2-CH\cdot CO_2H \end{array}$			139°/20 mm.	
Δ^4-Tetrahydro-o-toluic acid	 $\begin{array}{l} CH-CH_2-CH\cdot CH_3 \\ \| \qquad\qquad\quad \mid \\ CH-CH_2-CH\cdot CO_2H \end{array}$			135°/12 mm.	
Δ^5-Tetrahydro-o-toluic acid	 $\begin{array}{l} CH_2-CH_2-CH\cdot CH_3 \\ \mid \qquad\qquad\quad \mid \\ CH=CH-CH\cdot CO_2H \end{array}$		60–62° (trans)	145–146°/ 20 mm. (cis)	
Δ^6-Tetrahydro-o-toluic acid	 $\begin{array}{l} CH_2-CH_2-CH\cdot CH_3 \\ \mid \qquad\qquad\quad \mid \\ CH_2-CH=C\cdot CO_2H \end{array}$		79–80°		
Δ^1-Tetrahydro-m-toluic acid	 $\begin{array}{l} CH_2\cdot CH(CH_3)\cdot CH \\ \mid \qquad\qquad\quad \| \\ CH_2-CH_2-C\cdot CO_2H \end{array}$		26°		
Δ^2-Tetrahydro-m-toluic acid	 $\begin{array}{l} CH_2.C(CH_3)=CH \\ \mid \qquad\qquad\quad \mid \\ CH_2-CH_2 \quad CH\cdot CO_2H \end{array}$			123°/7 mm	— 49·7°
Δ^3-Tetrahydro-m-toluic acid	 $\begin{array}{l} CH=C(CH_3)\cdot CH_2 \\ \mid \qquad\qquad\quad \mid \\ CH_2-CH_2-CH\cdot CO_2H \end{array}$			138–140°/ 18 mm.	+ 108° — 98·6°
Δ^4-Tetrahydro-m-toluic acid	 $\begin{array}{l} CH-CH(CH_3)-CH_2 \\ \| \qquad\qquad\quad \mid \\ CH-CH_2-CH\cdot CO_2H \end{array}$			142–145°/ 20 mm. 142°/20mm.	+ 33·1° — 30·9°
Δ^5-Tetrahydro-m-toluic acid	 $\begin{array}{l} CH_2-CH(CH_3)-CH_2 \\ \mid \qquad\qquad\quad \mid \\ CH=CH-CH\cdot CO_2H \end{array}$			143–146°/ 20 mm.	
Δ^6-Tetrahydro-m-toluic acid	 $\begin{array}{l} CH_2-CH(CH_3)-CH_2 \\ \mid \qquad\qquad\quad \mid \\ CH_2-CH=C\cdot CO_2H \end{array}$	62–64°			+ 40·1° —35·8°
Δ^1-Tetrahydro-p-toluic acid	 $\begin{array}{l} CH_3CH-CH_2-CH \\ \mid \qquad\qquad\quad \| \\ CH_2-CH_2-C\cdot CO_2H \end{array}$	d-136–137° l-133–134°			+ 150·1° —100·8°
Δ^3-Tetrahydro-p-toluic acid	 $\begin{array}{l} CH_3C-CH-CH_2 \\ \mid \qquad\qquad\quad \mid \\ CH_2-CH_2-CH\cdot CO_2H \end{array}$	99°	98–99°		+ 55° — 58°

Δ^1-Tetrahydro-2,6-xylic acid, m.p. 90° (*Noyes*, Am. Chem. J. 22, 1). The isomeric **cyclogeranic acids,** $C_{10}H_{16}O_2$, are described with the Terpenes p. 207.

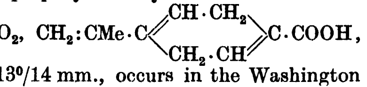
3,3,5-Trimethyl-tetrahydrobenzoic acid, m.p. 140°, b.p. 154°/16 mm., is formed from the cyanohydrin of dihydro-isoacetophorone (p. 110) by hydrolysis and elimination of water (Germ. Pat. 141,699).

(a_3) Dihydrobenzoic Acids.—**$\Delta^{1,3}$-Dihydrobenzoic acid,**



m.p. 95°, is produced in the oxidation of dihydrobenzaldehyde with Ag_2O (p. 124). A different **dihydrobenzoic acid,** m.p. 73°, is obtained from Δ^2-tetrahydrobenzoic acid dibromide (*Aschan*, Ber. **24**, 2622). **$\Delta^{2,6}$-Dihydro-o-toluic acid,** m.p. 175°, is obtained from the corresponding phthalide with HI and P (*Mazza*, Gazz. **57**, 300). **Dihydrocumic acid,** *p-isopropyl-dihydrobenzoic acid*, $C_6H_6(C_3H_7)COOH$, m.p. 130–133°, is formed when nopinic acid, an oxidation-product of β-pinene (p. 256), is boiled with sulphuric acid (*Baeyer*, Ber. **29**, 1926).

4-Isopropenyl-$\Delta^{1,4}$-cyclohexadiene-1-carboxylic acid, *dehydro-perillic acid*, $C_{10}H_{12}O_2$,

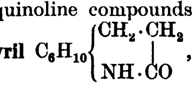


m.p. 88°, *methyl ester* b.p. 112–113°/14 mm., occurs in the Washington cedar *Thuja plicata* of western America and is toxic for the fungus *Fomes annosus*. Its constitution is established by the following facts. Hydrogenation gives **hexahydrocumic acid,** m.p. 150–152°, while HCl causes isomeric change into cumic acid, m.p. 116°. The exaltation of the molar refraction indicates two conjugated double bonds, an assumption which is supported by the fact that the compound is reduced by Na + EtOH. From the products of ozonisation, formaldehyde, formic acid and β,γ-diketo-valeric acid (p-nitrophenylosazone, m.p. 295°), the positions of the three double bonds, as shown in the formula above, follow (*Sowder*, Ind. Eng. **21**, 981; *Anderson*, *Sherrard*, Am. **55**, 3813).

(a_4) Cyclohexyl-, Cyclohexenyl- and Cyclohexadienyl-Fatty Acids.—**Cyclohexyl-acetic acid,** $C_6H_{11}\cdot CH_2CO_2H$, m.p. 33°, b.p. 110–112°/3 mm., is obtained from cyclohexyl-malonic acid, from hexahydrobenzyl chloride or iodide with Mg and CO_2 (*Gutt*, Ber. **40**, 2067), or from sodium mandelate, which on reduction loses its side chain OH-group (*Ipatiev*, Ber. **59**, 306), and also from phenylacetic acid by catalytic reduction (*Adams*, Am. **50**, 1970). **d(—)-α-Amino-cyclohexyl-acetic acid,** m.p. > 300°, is obtained from d(—)-α-amino-phenylacetic acid by hydrogenation (*Reihlen*, Ann. **523**, 208). **Cyclohexyl-propionic acid,** $C_6H_{11}\cdot CH_2CH_2COOH$, b.p. 112–114°/4 mm., from hexahydrobenzyl-malonic acid; *amide* m.p. 120° (*Zelinsky*, Ber. **41**, 2676). **Cyclohexyl-isobutyric acid,** m.p. 62–63°, from Δ^1-cyclohexenyl-isobutyric acid (p. 134).

Derivatives of *2-amino-cyclohexyl-acetic* and *-propionic acids* result from oxidising decahydro-quinoline compounds with $KMnO_4$.

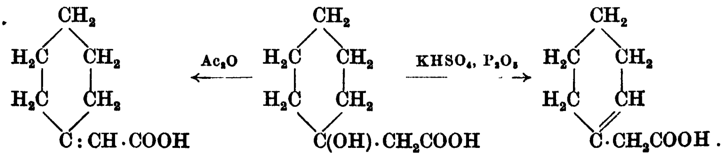
Octohydro-carbostyril



$$C_6H_{10}\begin{cases} CH_2\cdot CH_2 \\ \quad | \qquad\ \ | \\ NH\cdot CO \end{cases}$$

, m.p. 151°, is poisonous (*Bamberger*, Ber. **27**, 1472).

Cyclohexenyl-fatty acids are formed by elimination of water from the corresponding 1,1-cyclohexanol fatty acids or their esters, obtained by the action of bromo-aliphatic esters and zinc on cyclohexanones. According to the dehydrating agents used, P_2O_5 or $KHSO_4$ on the one hand, and formic acid or Ac_2O on the other, either the ring-unsaturated fatty acids, or the isomeric cyclohexylidene fatty acids, with semicyclic double bonds, are obtained:



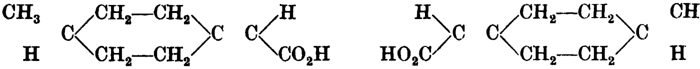
On heating both series of acids lose CO_2 and change into alkylidene-cyclohexanes (p. 94) (*Wallach*, Ann. **365**, 255).

Cyclohexylidene fatty acids are also obtained, though in bad yield, from cyclohexanones and malonic acid with pyridine (*Dutt*, J. Ind. ch. Soc. **1**, 297). Alkali causes isomeric changes into cyclohexenyl-fatty acids, with 1,1-hydroxy-fatty acids (see above) as intermediates (*Linstead*, J. **1927**, 362).

The cyclohexenones, which are readily obtained synthetically (p. 114), react with zinc and ethyl bromoacetate to give, not hydroxy-acids, but cyclohexadiene-carboxylic acids, which probably contain both double bonds in the ring. When heated, they lose CO_2 and hydrocarbons derived from dihydro-benzene are formed (*Wallach*, Ann. **323**, 136).

Δ^1-Cyclohexenyl-acetic acid, m.p. 38°. On oxidation with $KMnO_4$ *Δ^1-acetyl-cyclopentene* is formed, the intermediate being probably an aldehydo-ketonic acid (*Perkin*, *Wallach*, Ber. **42**, 145). Lactone, see *v. Braun*, Ann. **465**, 52. **Δ^2-Cyclohexenyl-acetic acid,** m.p. 12° (*Eijkman*, Chem. Weekbl. **6**, 699). **4-Methyl-Δ^1-cyclohexenyl-acetic acid,** m.p. 42° (*Harding*, *Haworth*, *Perkin*, J. **93**, 1943). **1-Methyl-Δ^3-cyclohexenyl-4-acetic acid,** m.p. 40·5–41° (*Perkin*, *Pope* and *Wallach*, J. **95**, 1793). **Δ^1-Cyclohexenyl-isobutyric acid,** m.p. 72°.

Cyclohexylidene-acetic acid, $(CH_2)_5 > C{:}CHCOOH$, m.p. 92°. **4-Methyl-cyclohexylidene-acetic acid,** m.p. 66° (inactive), has a special theoretical interest, since, without containing an asymmetric carbon atom, it can be resolved, by means of its brucine salt, into two optically active enantiomorphs, m.p. 52·5–53°, $[\alpha]_D \pm 81°$. The optical activity is arises from the fact that the structure of the molecule as a whole is enantiomorphous. It can be represented by the formula



in which the bonds in the plane of the paper are indicated by solid lines, and those in the plane at right angles to the paper by dotted lines. The Me and H thus lie on opposite sides of the plane of the paper, and the molecule contains no plane of symmetry; in other words, object and mirror image cannot coincide (*Perkin*, *Pope* and *Wallach*, J. **95**, 1793; cf. I, p. 44). For higher cyclohexenyl-fatty acids see *v. Braun*, Ann. **465**, 52.

β-Cyclohexyl-acrylic acid, *hexahydro-cinnamic acid* $C_6H_{11}CH{:}CH{\cdot}COOH$, m.p. 57–58°, from hexahydro-benzaldehyde, malonic acid and pyridine, also by the action of NaOBr on hexahydro-benzylidene-acetone which is obtained from the same aldehyde and acetone (*Sircar*, J. **1928**, 54).

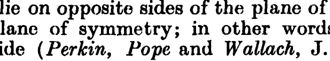
Cyclohexadienyl fatty acids: — **1,3-Methyl-cyclohexadienyl-acetic acid,** $MeC_6H_6CH_2CO_2H$, m.p. 171° from 3-methylcyclohexenone. **1,5-Dimethyl-cyclohexadienyl-3-acetic acid,** $Me_2C_6H_5CH_2CO_2H$, m.p. 151°, b.p. 170°/15 mm., from 3,5-dimethylcyclohexenone (*Wallach*, Ann. **323**, 139).

Cyclohexyl-acetylene-carboxylic acids: **Cyclohexyl-propiolic acid,**

$$C_6H_{11}{\cdot}C{\vdots}C{\cdot}CO_2H,$$

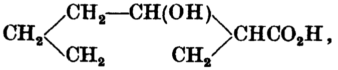
b.p. 152–153°/13 mm, from sodio-cyclohexyl-acetylene and CO_2 (*Jegorova*, C. 1912 I 1010). **Cyclohexyl-tetrolic acid,** $C_6H_{11}{\cdot}CH_2{\cdot}C{\vdots}C{\cdot}CO_2H$, m.p. 75°, from cyclohexyl-allylene (*Rességuier*, Bull. 7 (1910), 431). For homologous cyclohexyl-acetylene-carboxylic acids see *Bourguel*, Ann. Chimie **3** (1925), 325.

(b) Cyclohexane-hydroxy-acids, Hexahydro-hydroxybenzoic Acids.

— **1-Hydroxy-cyclohexane-carboxylic acid,** *1-hydroxy-hexahydro-benzoic acid,*  , m.p. 108–109° (*Passerini*, Gazz. **58**, 410) is formed when cyclohexanone (p. 109) is treated in ether with hydrocyanic and hydrochloric acids (*Tarbouriech*, C. r. **149**, 604). **3-Methyl-1-hydroxy-cyclohexane-carboxylic acid,** b.p. 164°/12 mm., has been obtained from *d*-3-methyl-cyclohexanone with HCN. A mixture of geometrical isomers is formed, from which an acid m.p. 97–98°, $\alpha_{4358} = -11{\cdot}01°$, has been isolated through its methyl ester (*Godchot*, C. r. **203**, 1042).

2-, 3- and 4-Cyclohexanol-carboxylic acids are formed by reduction of the hydroxy-benzoic acids or of the cyclohexanone-carboxylic acids with Na and EtOH. They usually occur in cis-trans isomeric forms, of which the cis forms of 3- and 4-cyclohexanol-carboxyl acids pass easily into lactones, when heated, with elimination of water.

2-Hydroxy-cyclohexane-carboxylic acid, *hexahydro-salicylic acid,*

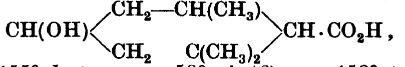


$$CH_2\left\langle\begin{matrix}CH_2-CH(OH)\\CH_2\qquad CH_2\end{matrix}\right\rangle CHCO_2H,$$

m.p. 111°, results from the action of nitrous acid upon hexahydro-anthranilic acid and from the reduction of cyclohexanone-2-carboxylic acid or ester with Na-amalgam (*Einhorn*, Ber. **27**, 2472, 2476). **3-Hydroxy-cyclohexane carboxylic acid,** m.p. cis 132–133°, trans 120°, by reduction of m-hydroxy-benzoic acid (id., Ann. **291**, 297; *Perkin*, J. **91**, 484; *Windaus*, Ber. **55**, 3981). **4-Hydroxy-cyclohexane carboxylic acid,** m.p. 121°, from 1,4-cyclohexanone-carboxylic acid (*Perkin*, J. **85**, 430). *Edson* has prepared the three acids from the three hydroxybenzoic acids (J. Soc. Chem. Ind. **53**, 138).

2-, 4-, 5- and 6-Methyl-3-hydroxy-cyclohexane-carboxylic acids have been obtained from the corresponding hydroxy-toluic acids (*Baudisch, Hibbert, Perkin*, J. **95**, 1870). **3-Methyl-4-hydroxy-cyclohexane-carboxylic acid,** m.ps. cis 140°, trans 116°, *lactone* m.p. 47°, from the corresponding keto-acid (*Fisher, Perkin*, J. **93**, 1882). **4-Methyl-4-hydroxy-cyclohexane-carboxylic acid,** m.p. 153°, *lactone* m.p. 70°, from cyclohexanone-4-carboxylic ester and MeMgI (*Perkin*, Proc. **1904**, 86).

Hydroxy-dihydro-cyclogeranic acid, *δ-hydroxy-cyclogeraniolane-carboxylic acid,*



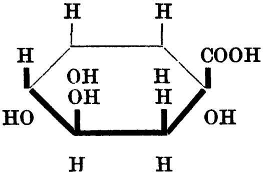
$$CH(OH)\left\langle\begin{matrix}CH_2-CH(CH_3)\\CH_2\qquad C(CH_3)_2\end{matrix}\right\rangle CH{\cdot}CO_2H,$$

cis (α) m.p. 145°, trans (α) m.p. 155°, *lactone* m.p. 58°, cis (β) m.p. 158°, trans (β) m.p. 38°, contains three asymmetric carbon atoms and hence exists in four inactive stereoisomeric forms, all of which are obtained by reducing isophorone-carboxylic ester with Na and EtOH. With dehydrating agents they all are converted, more or less easily, into Δ^3-cyclogeranic acid (p. 207) (*Merling*, Ann. **366**, 151). **3,5,5-Trimethyl-hexahydro-salicylic acid,** m.p. 180°, b.p. 204°/10 mm., from trimethyl-2-cyclohexanone-carboxylic acid (p. 138) (Germ. Pat. 142,139).

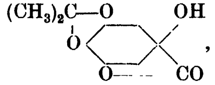
Hexahydro-phthalide, cis and trans, b.p. of both 134–138°/25 mm., is formed by heating the corresponding hydroxy-acid (p. 131), or by heating the Ag-salt of the cis or trans hexahydro-homophthalic acids with I_2 (*Windaus*, Ber. **55**, 3986). For substituted hexahydro-phthalides see *Berlingozzi*, Gazz. **57**, 248, 264. **Hexahydro-isophthalide,** a viscous oil, b.p. 111–115°/8 mm., by reduction (with Al-amalgam or catalytically) of hexahydro-isophthalic anhydride (*Komppa*, Ann. **521**, 257).

Hexahydro-dihydroxy-benzoic acid, from Δ^1-tetrahydro-benzoic acid dibromide (*Aschan*, Ann. **271**, 280). **Hexahydro-trihydroxy-benzoic acid,** *dihydroshikimic acid,* $(HO)_3C_6H_8{\cdot}CO_2H$, m.p. 176–178°, is obtained when shikimic acid (p. 136) is reduced with sodium amalgam.

Hexahydro-1,3,4,5-tetrahydroxy-benzoic acid, *quinic acid* $(HO)_4{\cdot}C_6H_7{\cdot}CO_2H$, m.p. 162°, optically active, is present in the true cinchona bark, in coffee beans, in bilberry, and, in small quantities, in hay and sugar-beet (*v. Lippmann*, Ber. **34**, 1159). It is obtained as a secondary product in the preparation of quinine by extracting the quinine bark. When its calcium salt has been purified by recrystallisation, the acid is liberated by oxalic acid. Its configuration, which was established by *Fischer* (Ber. **65**, 1009; id., Angew. **45**, 431), is:



The acid decomposes on distillation into phenol, hydroquinone, benzoic acid and salicylaldehyde. When boiled with water and lead peroxide, it gives hydroquinone, while MnO_2 and sulphuric acid convert it into quinone. Protocatechuic acid (vol. III) is formed when it is fused with caustic potash or soda. Bacteria decompose calcium quinate into protocatechuic acid, but if air is excluded during the fermentation, the only products are formic acid, acetic acid and propionic acid. Quinic acid is reduced by hydriodic acid to benzoic acid, and degraded to citric acid by periodic acid (*Fischer*, Helv. **17**, 1196). When it is treated with acetone, water is eliminated between the COOH-group and the OH in the 3-position, and acetone condenses with the OH groups in 4- and 5-positions, forming a *mono-acetone compound* of



quinic lactone, m.p. 140–141°, which gives a *mono-benzoyl compound*, m.p. 140°, with benzoyl chloride and pyridine. With hot dilute mineral acids acetone is set free and *quinic lactone* (see below) and *benzoyl-quinic lactone*, m.p. 148°, are formed (*Fischer*, Ber. **54**, 781; **60**, 485; *Mazza*, Gazz. **57**, 292).

Calcium salt, $(C_7H_{11}O_6)_2Ca + 10H_2O$. *Methyl ester* m.p. 120°, *amide* m.p. 132°, *tetramethyl ether-methyl ester* m.p. 56–58, (*Herzig*, Arch. Pharm. **258**, 61), *tetracetyl-ethyl ester*, $C_6H_7(O{\cdot}COMe)_4{\cdot}CO_2Et$, m.p. 135° (*Erwig*, Ber. **22**, 1462). For other derivatives see *Fischer*, Ber. **54**, 775.

Inactive quinic acid is produced when its lactone, quinide, is boiled with milk of lime. *Calcium salt*, $(C_7H_{11}O_6)_2Ca + 4H_2O$.

Quinic lactone, *quinide*, $C_7H_{10}O_5$, m.p. 198°, optically inactive, is formed as mentioned above, and also by heating ordinary optically active quinic acid to 220–240° (*Eijkman*, Ber. **24**, 1296).

Quinic acid forms a depside with caffeic acid (vol. III) which is known as **chlorogenic acid,** *3-caffoyl-quinic acid* (*Fischer*, Ber. **65**, 1037),

$$COOH[1]C_6H_7(OH)_3[1,4,5]{\cdot}[3]{\cdot}O{\cdot}CO{\cdot}CH{:}CH{\cdot}[1']C_6H_3(OH)_2[3',4'],$$

m.p. 206–207°; it occurs in the coffee beans also in the milky sap of *Ficus elastica* and *Castilloa el.* (*Gorter*, Rec. **31**, 281). Chlorogenic acid gives a sensitive colour reaction with alkali nitrite and NaOH (*Hopfner*, Chem.-Ztg. **56**, 991; *Griebel*, ib. **57**, 353; estimation in coffee beans ib. **57**, 875).

A **hexahydro-pentahydroxy-benzoic acid,** *dihydroxy-dihydro-shikimic acid*, $(HO)_5C_6H_6{\cdot}CO_2H$, which melts at 156° and is optically inactive, is formed by the action of aqueous baryta on dibromo-shikimic acid. The latter, when evaporated with water, forms a *bromo-lactone* m.p. 295° (*Eijkman*, Ber. **24**, 1294).

Tetrahydro-hydroxy-benzoic acids: **2-(α-Hydroxyamyl)-Δ^2-tetrahydrobenzoic acid,** *sedanolic acid*, m.p. 88–89°, occurs as its lactone in the high-boiling fractions of the essential oil of celery. On heating it gives the lactone **sedanolide,** b.p. 85°/17 mm., which smells strongly of celery (*Ciamician*, Ber. **30**, 498, 1420).

Tetrahydro- and dihydro-phthalides and the odour of their alkyl substitution products have been studied by *Berlingozzi*, Gazz. **57**, 264; **61**, 886, and by *Komppa*, Ann. **521**, 257.

Δ^1-Tetrahydro-3,4,5-trihydroxy-benzoic acid, *shikimic acid*,

$$(HO)_3C_6H_6{\cdot}CO_2H,$$

m.p. 184°, occurs in the fruit of *Illicium religiosum* (cf. shikimol, vol. III). Its dihydro- and dihydroxy-dihydro-derivatives have been described above.

Cyclohexanol-fatty acids: **Cyclohexanol-1-acetic acid,**

$$C_5H_{10}{:}C(OH)\cdot CH_2CO_2H,$$

m.p. 63°. **4-Methyl-cyclohexanol-1-acetic acid,** $CH_3\cdot C_5H_9{:}C(OH)\cdot CH_2\cdot CO_2H$, α-acid, m.p. 141°, β-acid, m.p. 90°. **4-Methyl-cyclohexanol-1-α-propionic acid,** $CH_3\cdot C_5H_9{:}C(OH)\cdot CH(CH_3)\cdot CO_2H$, m.p. 110°. These esters are prepared by condensation of cyclohexanones with bromo-aliphatic esters and zinc (p. 133) (*Wallach*, Ann. **360**, 26; **365**, 261; *Becherer*, Helv. 8, 184).

Hexahydro-mandelic acid, $C_6H_{11}\cdot CH(OH)\cdot COOH$, m.p. 166°, from cyclohexyl-acetaldehyde cyanhydrin (*Zelinsky*, Ber. **41**, 2677). **Hexahydro-atrolactic acid,** $C_6H_{11}C(OH)(Me)COOH$, m.p. of the racemic form 101·5°, is obtained by hydrogenating atrolactic acid (*Freudenberg*, Ann. **501**, 217).

Cyclohexyl-glycidic esters, such as $[CH_2]_5{:}\overline{C\cdot O\cdot C}H\cdot CO_2Et$, b.p. 128°/17 mm., and $[CH_2]_5{:}\overline{C\cdot O\cdot C}(CH_3)CO_2Et$, b.p. 155°/40 mm., are formed by condensing cyclohexanones with chloro-acetic ester or α-chloro-propionic ester by means of NaOEt. Similarly, Δ^1-tetrahydro-acetophenone yields **methyl-tetrahydro-phenyl-glycidic ester,** $C_6H_9.\overline{C(Me)O\cdot C}H\cdot CO_2Et$. The glycidic acids resulting from the hydrolysis of these esters readily decompose into CO_2 and aldehydes or ketones (pp. 122, 124) (*Darzens*, C. r. **142**, 714; **144**, 1123; **151**, 758).

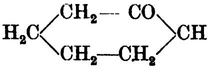
Some polyene-carboxylic acids: e.g. **azafrin,** $C_{27}H_{38}O_4$, are also hydroxy-fatty acids of the cyclohexane series and are described with the Natural Colouring Matters (p. 413).

Hexahydro-phenylglycine-o-carboxylic acid, $C_6H_{10}(COOH)\cdot NHCH_2COOH$, m.p. 234°, from phenylglycine-o-carboxylic acid (vol. III) with H_2 and Pt-black, titrates as a monobasic acid, $C_6H_{10}(COO^-)\cdot \overset{+}{N}H_2\cdot CH_2\cdot COOH$. *Dimethyl ester* m.p. 60°. The *ethyl ester* gives *hexahydro-indoxylic ester*, m.p. 95° (vol. IV) when treated with NaOEt (*Vorlander*, Ber. **59**, 2075).

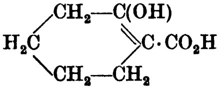
(c) Keto-cyclohexane-(-hexene-)monocarboxylic Acids. —

1,2-Cyclohexanone carboxylic acids and their esters are formed: (1) by cyclic aceto-acetic ester condensation of pimelic esters and their alkyl substitution products by means of sodium (*Dieckmann*, Ann. **317**, 27); (2) by condensing cyclohexanones with oxalic ester; the cyclohexanone-glyoxylic esters so formed lose CO when heated (*Kotz*, Ann. **350**, 211); (3) by the action of sodamide and CO_2 on cyclohexanones in ether solution (*Gardener*, J. **97**, 1764).

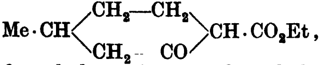
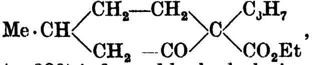
1,2-Cyclohexanone-carboxylic acid,

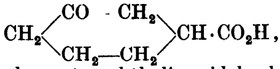


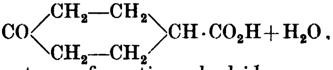
$H_2C\langle{}^{CH_2-CO}_{CH_2-CH_2}\rangle CH\cdot CO_2H$, or in the enolic form



$H_2C\langle{}^{CH_2-C(OH)}_{CH_2-CH_2}\rangle C\cdot CO_2H$, m.p. 81–82° with loss of CO_2. The *ethyl ester*, b.p. 107°/11 mm., is obtained as above; it resembles 2-cyclopentanone-carboxylic ester (p. 68) in being a cyclic analogue of acetoacetic ester, and at ordinary temperature the ester contains 76% of the enolic form (*Dieckmann*, Ber. **55**, 2470). It is decomposed by dilute sulphuric acid into cyclohexanone, and by boiling alcoholic potash into pimelic acid. With NaOEt and MeI it gives **1-methyl-1,2-cyclohexanone-carboxylic ester,** b.p. 108°/11 mm., which is decomposed to α-methylpimelic acid by alcoholic potash. These β-keto-esters yield bicyclic pyrazolone derivatives with hydrazines. With NH_3 1,2-cyclohexanone-carboxylic ester gives *tetrahydro-anthranilic ester*, $C_6H_8(NH_2)CO_2R$, m.p. 74° (*Dieckmann*, Ann. **317**, 93); the free acid of this ester has also been obtained from anthranilic acid by reduction with Na and amyl alcohol (*Mazza*, Gazz. **57**, 292). With benzamidines *tetrahydro-quinazolines* (vol. IV) are formed.

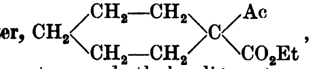
Special interest attaches to **4-methyl-1,2-cyclohexanone-carboxylic ester,**  $\mathrm{Me{\cdot}CH}\left\langle\begin{array}{l}\mathrm{CH_2{-}CH_2}\\ \mathrm{CH_2{-}CO}\end{array}\right\rangle\mathrm{CH{\cdot}CO_2Et}$, b.p. 123°/13 mm., obtained from ethyl β-methyl-pimelate or 1,3-methyl-cyclohexanone-glyoxylate; with sodium and isopropyl iodide it gives **4-methyl-1-isopropyl-1,2-cyclohexanone-carboxylic ester,**  $\mathrm{Me{\cdot}CH}\left\langle\begin{array}{l}\mathrm{CH_2{-}CH_2}\\ \mathrm{CH_2{-}CO}\end{array}\right\rangle\mathrm{C}\left\langle\begin{array}{l}\mathrm{C_3H_7}\\ \mathrm{CO_2Et}\end{array}\right.$, b.p. 146°/14 mm., from which menthone (p. 230) is formed by hydrolysis with dilute sulphuric acid (*Straus*, Ann. **342**, 198). *d*-**3-Methyl-1,2-cyclohexanone-carboxylic acid,** m.p. 103°, inactive form m.p. 100°. **5-Methyl-1,2-cyclohexanone-carboxylic acid,** m.p. 101°, is prepared by method (3). **3,5,5-Trimethyl-1,2-cyclohexanone-carboxylic acid,** m.p. 111° decomp., is formed from dihydro-isoacetophorone by treatment with CO_2 and Na in ether (Germ. Pat. 136,873).

1,3-Cyclohexanone-carboxylic acid,  $\mathrm{CH_2}\left\langle\begin{array}{l}\mathrm{CO{-}CH_2}\\ \mathrm{CH_2{-}CH_2}\end{array}\right\rangle\mathrm{CH{\cdot}CO_2H}$, m.p. 74°, can be obtained from tetrahydro-hydroxy-terephthalic acid by heating to 115°, or on boiling with water, or by oxidation of the ester of 1,3-hydroxy-hexahydro-benzoic acid with sodium bichromate (*Dobson*, J. **95**, 2010).

1,4-Cyclohexanone-carboxylic acid,  $\mathrm{CO}\left\langle\begin{array}{l}\mathrm{CH_2{-}CH_2}\\ \mathrm{CH_2{-}CH_2}\end{array}\right\rangle\mathrm{CH{\cdot}CO_2H+H_2O}$, m.p. 68°, has been prepared by the action of acetic anhydride upon $\alpha,\gamma,\varepsilon$-pentane-tricarboxylic acid and subsequent distillation. This acid has served as starting material for the synthesis of α-terpineol (p. 223) and dipentene (p. 209) (*Perkin*, J. **85**, 416). **3-Methyl-1,4-cyclohexanone-carboxylic acid,** m.p. 94° (*Fisher, Perkin*, J. **93**, 1876).

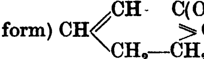
A number of γ-keto-carboxylic acids have been obtained by reducing the corresponding 1,4-cyclohexenone-carboxylic esters (see below) with hydrogen and colloidal Pd (*Skita*, Ber. **42**, 1627). **2-Methyl-1,4-cyclohexanone-carboxylic ethyl ester,** b.p. 128°/15 mm. **Dihydro-isophorone-carboxylic ester** occurs in two cis-trans isomeric forms: α-form, m.p. 44°, b.p. 125°/9 mm.; β-form, liquid, b.p. 137°/12 mm.; the free acids, α, m.p. 127°, and β, m.p. 119°, can also be obtained by oxidation of the hydroxy-dihydro-cyclogeranic acids (p. 135). They give the trans forms of these acids when reduced with sodium and alcohol.

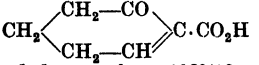
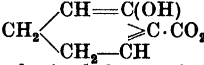
1-Methyl-cyclohexane-3-one-4-acetic acid, *semicarbazone* m.p. 116°, is obtained by heating the corresponding malonic acid to 85°. *Lactone* m.p. 104–106° (*Kötz*, J. pr. **110**, 118).

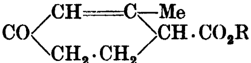
1-Acetyl-cyclohexane-carboxylic ester,  $\mathrm{CH_2}\left\langle\begin{array}{l}\mathrm{CH_2{-}CH_2}\\ \mathrm{CH_2{-}CH_2}\end{array}\right\rangle\mathrm{C}\left\langle\begin{array}{l}\mathrm{Ac}\\ \mathrm{CO_2Et}\end{array}\right.$, b.p. 241–245°, is formed from 1,5-dibromo-pentane and ethyl sodio-acetoacetate; on boiling with alcoholic potash it yields hexahydro-acetophenone (p. 124) (*v. Braun*, Ber. **40**, 3945). Similarly, **2-methyl-1-acetyl-cyclohexane-carboxylic ester** is obtained from 1,5-dibromo-hexane and ethyl sodio-acetoacetate (*Freer, Perkin*, Ber. **21**, 737).

Hexahydrobenzoyl-acetic ester, $C_6H_{11}{\cdot}CO{\cdot}CH_2CO_2Et$, b.p. 136°/18 mm., from hexahydrobenzoic ester, acetic ester and sodium (*Wahl*, Bull. **3** (1908), 957). δ-**Hexahydrobenzoyl-n-valeric acid,** m.p. 58°, is formed in the oxidation of cyclohexyl-cyclohexanone (*Wallach*, Ann. **389**, 169).

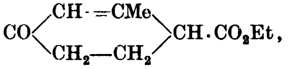
Cyclohexyl-acetoacetic ester, $C_6H_{11}{\cdot}CH(Ac)CO_2Et$, b.p. 126°/14 mm., is obtained, in bad yield, from iodo-cyclohexane and ethyl sodio-acetoacetate (*Hell*, Ber. **42**, 2232).

Δ^3-1,2-Cyclohexenone-carboxylic acid, *$\Delta^{1,3}$-dihydro-salicylic acid* (enolic form)  $\mathrm{CH}\begin{matrix}\diagup\mathrm{CH\cdot C(OH)}\\ \diagdown\mathrm{CH_2{-}CH_2}\end{matrix}\!\!\geqslant\mathrm{C\cdot COOH}$, easily loses CO_2; it is obtained from Δ^2-cyclohexenone with CO_2 and Na, or by condensation with oxalic ester followed by loss of CO (*Kotz*, J. pr. **80**, 506).

Δ^6-1,2-Cyclohexenone-carboxylic acid, *$\Delta^{2,6}$-dihydro-salicylic acid*  $\mathrm{CH_2}\begin{matrix}\diagup\mathrm{CH_2{-}CO}\diagdown\\ \diagdown\mathrm{CH_2{-}CH}\diagup\end{matrix}\mathrm{C\cdot CO_2H}$ and  $\mathrm{CH_2}\begin{matrix}\diagup\mathrm{CH{=}C(OH)}\\ \diagdown\mathrm{CH_2{-}CH}\end{matrix}\!\!\geqslant\mathrm{C\cdot CO_2H}$, m.p. 128°; its *ethyl ester*, b.p. 103°/12 mm., is obtained from ethyl 1,2-cyclohexanone-carboxylate by bromination to ethyl α-bromo-1,2-cyclohexanone-carboxylate, b.p. 144°/13 mm., and elimination of HBr by boiling with aniline. On heating with soda-lime the acid breaks up into CO_2 and Δ^2-cyclohexenone (*Kotz*, J. pr. **80**, 494; Ann. **385**, 200).

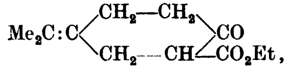
Δ^2-1,4-Cyclohexenone-carboxylic esters, such as  $\mathrm{CO}\begin{matrix}\diagup\mathrm{CH{=}C{-}Me}\diagdown\\ \diagdown\mathrm{CH_2\cdot CH_2}\diagup\end{matrix}\mathrm{CH\cdot CO_2R}$, are obtained by the action of sodium ethoxide upon alkylidene-bis-acetoacetic ester, one carboxyl group being lost. They contain the same grouping as glutaconic ester (I, 575), and can therefore, like the latter, be alkylated with NaOEt and alkyl iodide. The esters occur in a neutral form insoluble in alkali, and an acid form soluble in alkali. The former may be converted into the latter by NaOEt. Reduction with H_2 and colloidal Pd produces 1,4-cyclohexanone-carboxylic esters. The cyclohexenone-carboxylic acids easily break up into CO_2 and Δ^2-cyclohexenones (p. 114).

2-Methyl-Δ^2-1,4-cyclohexenone-carboxylic ester,



$$\mathrm{CO}\begin{matrix}\diagup\mathrm{CH{=}CMe}\diagdown\\ \diagdown\mathrm{CH_2{-}CH_2}\diagup\end{matrix}\mathrm{CH\cdot CO_2Et},$$

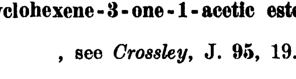
b.p. 155°/18 mm., is obtained from methylene iodide and ethyl Na-acetoacetate or from ethyl methylene-bis-acetoacetate by the action of NaOEt (*Skita*, Ber. **41**, 2943); the addition product with bromine loses 2HBr and gives o-methyl-p-hydroxy-benzoic acid (*Rabe*, Ber. **38**, 969). **2,6-Dimethyl-Δ^2-1,4-cyclohexenone-carboxylic ester,** b.p. 140°/7 mm., from ethyl ethylidene-bis-acetoacetate (id. Ann. **342**, 344). **Isophorone-carboxylic ester,**



$$\mathrm{CO}\begin{matrix}\diagup\mathrm{CH{=}CMe}\diagdown\\ \diagdown\mathrm{CH_2{-}CMe_2}\diagup\end{matrix}\mathrm{CH\cdot CO_2Et},$$

b.p. 136–140°/10 mm., is formed by combination of ethyl sodio-acetoacetate and isopropylidene-acetoacetate. On hydrolysis isophorone (p. 116) is produced, and on reduction with Na+EtOH, a mixture of various stereoisomeric hydroxy-dihydro-cyclogeranic acids (p. 135).

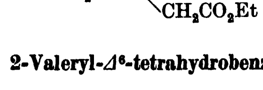
5-Isopropylidene-cyclohexane-2-one-1-carboxylic ester,



$$\mathrm{Me_2C{:}C}\begin{matrix}\diagup\mathrm{CH_2{-}CH_2}\diagdown\\ \diagdown\mathrm{CH_2{-}CH}\diagup\end{matrix}\mathrm{CO}\quad\mathrm{CH{-}CO_2Et},$$

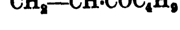
has been obtained by cyclic acetoacetic ester condensation from γ-isopropylidene-pimelic ester (*Perkin*, J. **91**, 1744).

5,5-Dimethyl-Δ^1-cyclohexene-3-one-1-acetic ester, b.p. 171°/22 mm.,



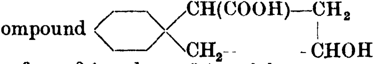
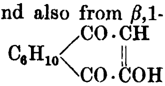
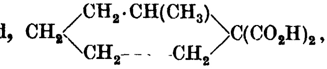
$$\mathrm{Me_2C}\begin{matrix}\diagup\mathrm{CH_2{-}CO}\diagdown\\ \diagdown\mathrm{CH_2\quad C}\diagup\end{matrix}\mathrm{CH}\quad\mathrm{C{-}CH_2CO_2Et}$$

, see *Crossley*, J. **95**, 19.

2-Valeryl-Δ^6-tetrahydrobenzoic acid, *sedanonic acid,*  $\mathrm{H_2C}\begin{matrix}\diagup\mathrm{CH_2{-}CH}\diagdown\\ \diagdown\mathrm{CH_2{-}CH\cdot COC_4H_9}\diagup\end{matrix}\mathrm{C\cdot COOH}$, m.p. 113°, occurs in celery oil (*Ciamician*, Ber. **30**, 503, 1419) and in the essential oil of the Chinese drug *Cnidium officinale* (*Murayama*, J. Pharm. Soc. Jap. **1923**, No. 493).

(B) Hydroaromatic Dicarboxylic Acids

(a_1) Cyclohexane-dicarboxylic Acids. — These acids show the behaviour of dialkyl-malonic acids, symm. dialkyl-succinic acids, symm. α-dialkyl-glutaric acids or symm. α-dialkyl-adipic acids, according to the relative position of the carboxyl groups.

Cyclohexane-1,1-dicarboxylic and **2-methyl-cyclohexane-1,1-dicarboxylic esters** have been made by the action of sodio-malonic ester on (methyl) 1,5-dibromopentane. The free acids lose CO_2 when heated and give hexahydrobenzoic acid and hexahydro-o-toluic acid. The free **1,1-cyclohexane-dicarboxylic acid,** m.p. 207° decomp., was first prepared by *Ingold* and *Thorpe* (J. **115**, 376; **123**, 865) from the spiro-compound  by oxidation with HNO_3, and also from β,1-carboxy-β,1-cyclohexane-acrylic acid or from the diketone  $C_6H_{10}\langle\begin{matrix}CO\cdot CH\\ \|\\ CO\cdot COH\end{matrix}$ with $KMnO_4$. **2-Methyl-cyclohexane-1,1-dicarboxylic acid,**  $CH_2\langle\begin{matrix}CH_2\cdot CH(CH_3)\\ CH_2 - CH_2\end{matrix}\rangle C(CO_2H)_2$, m.p. 147° (*Perkin*, J. **53**, 206).

Hexahydrophthalic Acids. — According to *Baeyer*'s theory (Ann. **258**, 145), which is based on the tetrahedral distribution of the groups attached to carbon, two geometrically isomeric hexahydrophthalic acids are possible. The isomerism is due to the different positions occupied by the carboxyls relative to the plane of the cyclohexane ring; hence the isomers are termed cis and trans forms (cf. p. 30 et al.). A general method of preparing o-, m- and p-hexahydrophthalic acids is from the dibromides of tetramethylene, trimethylene, ethylene, which are condensed with Na-compounds of ethane-, propane-, butane-ω,ω-tetra-carboxylic esters. The resulting cyclohexane-1,1–2,2, -1,1–3,3- and -1,1–4,4-tetracarboxylic acids are heated to remove $2CO_2$ (*Goldsworthy*, J. **1931**, 482).

Hexahydro-o-phthalic acid, *cyclohexane-1,2-dicarboxylic acid,* $C_6H_{10}(CO_2H)_2$, *cis* m.p. 192°, *anhydride* m.p. 32°, b.p. 145°/18 mm., *imide* m.p. 137°, and *trans* m.p. 222°, *anhydride* m.p. 143°, are produced together when Δ^4-tetrahydro-o-phthalic acid is reduced, or when 1,1,2,2-cyclohexane-tetracarboxylic acid is heated to 200° (*Goldsworthy*, l. c.). The cis acid is also obtained by hydrogenating Δ^1-tetrahydrophthalic acid (p. 141) and the trans acid by oxidising 2-methylol-hexahydrobenzoic acid (p. 131). Another way of preparing the trans compound, which is due to *Kon* and *Qudrat-I-Khuda* (J. **1926**, 3071), is from Δ^1-cyclohexenyl-methyl-ketone which is condensed with ethyl Na-malonate. The resulting decahydronaphthalene compound is then oxidised.

The cis acid is more soluble in water than the trans acid, and when heated with conc. HCl it passes into the trans acid. The anhydride of the latter is converted by heating for some time at 210–220° into the cis anhydride (*Baeyer*, Ann. **258**, 214). When the cis ester is heated with NaOEt it is converted quantitatively into the trans ester (*W. Huckel*, Ber. **58**, 449). The trans acid has been resolved by means of its quinine salt into optically active components, *d*- and *l-trans hexahydrophthalic acids,* $[\alpha]_D + 18{\cdot}2°$ and $-18{\cdot}5°$, m.p. 179–183°; *anhydride,* m.p. 164° (*Werner*, Ber. **32**, 3046). The cis acid is in the meso form and cannot be resolved; the anilic acid, however, has an asymmetric structure, and has been resolved by means of the cinchonidine salt (*Stoermer*, Ber. **65**, 413).

Cyclohexane-1,3-dicarboxylic acids, hexahydro-isophthalic acids, are both formed in the reduction of isophthalic acid (*Komppa*, C. 1933 II 865), and when 1,1,3,3-cyclohexane-tetracarboxylic acid is heated to 200–220°. The calcium salt of the cis acid is more sparingly soluble than that of the trans acid. The *cis acid*, m.p. 163°, is partly converted by heating to 180° with hydrochloric acid into the *trans acid*, m.p. 148°. Both acids give an *anhydride*, m.p. 187°, with acetyl chloride (*Komppa*, Ann. **521**, 242). The trans acid has been resolved by means of the strychnine salt into its optical antimers, m.p. 134°, $[\alpha]_D \pm 23°$ (*Boeseken*, Rec. **44**, 841).

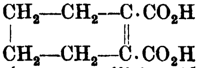
Cyclohexane-1,4-dicarboxylic acids, hexahydro-terephthalic acids can be obtained by reducing the hydrobromides of the tetrahydro-terephthalic acids in glacial acetic acid with zinc dust or catalytically, by ozonising 3,6-endoethylene-Δ^1-tetrahydrophthalic acid, obtained from 1,3-dihydrobenzene and dibromo-maleic anhydride with subsequent catalytic reduction (*Diels*, Ann. **478**, 149), or by heating cyclohexane-1,1,4,4-tetracarboxylic acid to 200–220°. The ozonisation method gives the cis acid, m.p. 171°, which is also formed from dicyclohexadiene (p. 193) by oxidation, while from cyclohexane-tetracarboxylic acid the trans acid, melting at 309°, is the chief product. The cis acid, when heated with hydrochloric acid to 180°, rearranges into the trans acid.

The three pairs of hexahydro-phthalic acids resemble fumaric and maleic acids, both in their solubilities and in the methods by which they can be interconverted. They are sometimes described as *maleinoid* and *fumaroid* modifications.

α-Bromo substitution products of these acids have been prepared from the acid chlorides by treatment with bromine, and also by diene condensation with bromo-maleic anhydride. Bromo-substituted hexahydro-dicarboxylic acids are also formed by the addition of HBr or Br_2 to tetra- and dihydro-dicarboxylic acids.

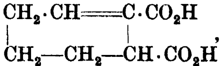
(a_2) Cyclohexene-dicarboxylic Acids, *tetrahydro-o-phthalic acids.*— Four structural isomers are possible, which differ in the position of the double bond. The two modifications in which neither of the two CO_2H groups is attached to a doubly bound C-atom can each exist in two geometrically isomeric forms.

Δ^1-Tetrahydro-o-phthalic acid,



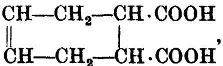
, m.p. 120°; the *anhydride* m.p. 74°, is formed when hydro-pyromellitic acid (vol. III) is distilled, or from the cyanhydrin of 1-cyclohexanone-2-carboxylic ester by hydrolysis and elimination of two mol. H_2O (*W. Huckel*, Ber. **67**, 1811). $KMnO_4$ oxidises it to adipic acid (*Baeyer*, Ann. **166**, 346; **258**, 203). When the anhydride is reduced in the presence of Ni at 220°–240°, there is no reduction of the ring, but one CO-group is reduced to CH_2, so that the corresponding *phthalide*, m.p. 73°, is formed; this on hydrolysis gives Δ^1-*tetrahydro-methylol-o-benzoic acid*, m.p. 85°. The hydrophthalides in which alkyl groups are attached to the lactone ring have the smell of celery (*Mazza*, Gazz. **57**, 300; *Berlingozzi*, C. 1927 II 255).

Δ^2=Δ^6-Tetrahydro-o-phthalic acid,



, m.p. 215°, *anhydride* m.p. 78°, has been obtained by the decomposition of sedanonic acid (p. 139; *Ciamician*, Ber. **30**, 503, 1419). It is also formed by boiling the Δ^1-acid with KOH, when the double bond shifts, and by the reduction of phthalic acid or $\Delta^{2,6}$-dihydrophthalic acid, when

trans-Δ^4-Tetrahydro-o-phthalic acid,

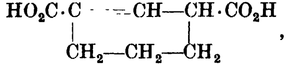


, m.p. 216°, *anhydride* m.p. 140°, is also formed. This can be separated from the Δ^2-acid by means of acetyl chloride, which in the cold converts the Δ^{4}-acid into the anhydride, but has no action on the Δ^{2}-acid (*Baeyer*, Ann. **258**, 211).

cis-Δ^{4}-Tetrahydro-o-phthalic acid, m.p. 166°, is formed when the $\Delta^{2,4}$-dihydro-acid is reduced and can be also obtained from its *anhydride*, m.p. 103–104°, which is formed when the anhydride of the trans Δ^{4}-acid is heated (id. Ann. **269**, 202). It can also be prepared by diene synthesis from maleic anhydride and butadiene in benzene (*Diels*, Ann. **460**, 113). Catalytic reduction converts the acid into cis hexahydro-o-phthalic acid (p. 140). *Diels* and *Alder* (l. c.; Ber. **62**, 2087) have prepared many methyl- and phenyl-substituted Δ^{4}-tetrahydrophthalic acids by the diene method from maleic anhydride and methyl-, phenyl- or diphenyl-butadienes, and also acids bridged by endo-methylene and endo-ethylene groups in the 3,6-positions (p. 192), from cyclopentadiene or 1,3-dihydro-benzene and maleic, citraconic, itaconic anhydrides or their derivatives. All these acids give hexahydrophthalic acids on catalytic reduction.

Three structurally isomeric *tetrahydro-isophthalic acids* are theoretically possible, of which one should occur as two geometrical isomers. Three acids are known, but there is still confusion here (*Perkin*, J. **87**, 293; *Farmer* and *Richardson*, J. **127**, 59; *Kon* and *Nandi*, J. **1933**, 1628).

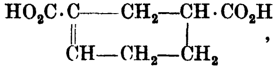
Δ^{1}=Δ^{2}-Tetrahydro-isophthalic acid,



$$\begin{array}{l} HO_2C\cdot C{=}CH—CH\cdot CO_2H \\ \qquad\quad |\qquad\qquad\quad | \\ \qquad CH_2—CH_2—CH_2 \end{array}$$

, m.p. 197—198°, from cyclohexanone-2 : 6-dicarboxylic acid by reduction, dehydration and hydrolysis. This acid is not formed in the reduction of isophthalic acid.

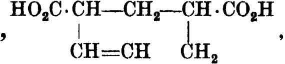
Δ^{3}=Δ^{6}-Tetrahydro-isophthalic acid,



$$\begin{array}{l} HO_2C\cdot C—CH_2—CH\cdot CO_2H \\ \qquad\quad \|\qquad\qquad\ \ | \\ \qquad CH—CH_2—CH_2 \end{array}$$

, m.p. 244°, is formed from the Δ^{4}-acid on boiling with concentrated potash.

cis-Δ^{4}=Δ^{5}-Tetrahydro-isophthalic acid,



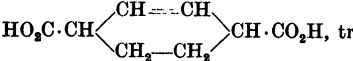
$$\begin{array}{l} HO_2C\cdot CH—CH_2—CH\cdot CO_2H \\ \qquad\quad |\qquad\qquad\quad | \\ \qquad CH{=}CH\qquad CH_2 \end{array}$$

, m.p. 165°, is formed in the reduction of isophthalic acid with sodium amalgam.

The *anhydride*, m.p. 78°, formed by heating any of the three tetrahydro-isophthalic acids with acetic anhydride, is derived from the Δ^{2}- or Δ^{3}-acid, and not from the Δ^{1}-acid, as was formerly believed (*Bredt*, J. pr. **147**, 27).

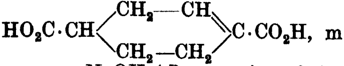
Tetrahydro-terephthalic acids theoretically can exist in two structurally isomeric forms, which differ in the position of the double bond; one of them can occur in two stereoisomeric modifications (see above).

Δ^{2}-Tetrahydro-terephthalic acid,



, trans m.p. 228°, cis m.p. 161°, *l*-trans m.p. 222°. Both geometrical isomers result from the reduction of $\Delta^{1,3}$- and $\Delta^{1,5}$-dihydroterephthalic acids (*Baeyer*, Ann. **251**, 273). The cis acid is much more readily soluble in water than the trans acid. Both are oxidised to succinic acid by $KMnO_4$, and both are converted into

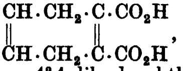
Δ^{1}-Tetrahydro-terephthalic acid,



, m.p. >300° (sublimes), by boiling with aqueous NaOH (*Baeyer*, Ann. **258**, 7); cf. the similar change of β,γ-hydromuconic acid into the α,β-acid (I, 577).

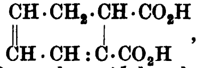
(a_3) Cyclohexadiene-dicarboxylic Acids. — Six structural isomers of *dihydro-o-phthalic acids* are possible, according to the position of the double bonds, one of which can occur in two stereoisomeric modifications.

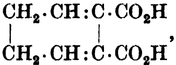
$\Delta^{1,4}$-Dihydro-o-phthalic acid,

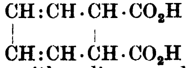


$$\begin{array}{l} CH\cdot CH_2\cdot C\cdot CO_2H \\ \|\qquad\qquad \| \\ CH\cdot CH_2\cdot C\cdot CO_2H \end{array}$$

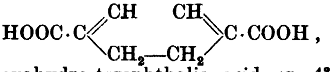
, m.p. 153°, *anhydride* m.p. 134°, is produced by boiling $\Delta^{2,4}$-dihydrophthalic acid with acetic anhydride for some time (*Baeyer*, Ann. **269**, 204).

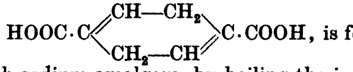
$\Delta^{2,4}$-Dihydro-o-phthalic acid,  $\begin{array}{l} CH\cdot CH_2\cdot CH\cdot CO_2H \\ \| \qquad\qquad | \\ CH\cdot CH:C\cdot CO_2H \end{array}$, m.p. 179°; the *anhydride,* m.p. 103°, is produced from the acid by the action of acetic anhydride in the cold. The acid is obtained by boiling $\Delta^{2,6}$-dihydro-o-phthalic dihydrobromide with potash in MeOH.

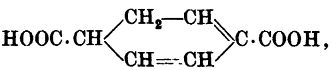
$\Delta^{2,6}$-Dihydro-o-phthalic acid,  $\begin{array}{l} CH_2\cdot CH:C\cdot CO_2H \\ | \qquad\qquad | \\ CH_2\cdot CH:C\cdot CO_2H \end{array}$, m.p. 215°, *anhydride* m.p. 83°. The acid results from the reduction of phthalic anhydride with sodium amalgam in alkaline solution (*Baeyer*, Ann. **269**, 152, 194), and from boiling the $\Delta^{2,4}$- or $\Delta^{3,5}$-acid with aqueous NaOH (*Proost*, Ber. **27**, 3185).

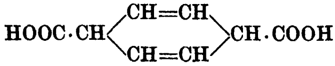
trans-**$\Delta^{3,5}$-Dihydro-o-phthalic acid,**  $\begin{array}{l} CH:CH\cdot CH\cdot CO_2H \\ | \qquad\qquad | \\ CH:CH\cdot CH\cdot CO_2H \end{array}$, m.p. 210°, is obtained by reducing phthalic anhydride with sodium amalgam in acetic acid solution. The acid has been resolved into its optical antimers by means of its strychnine salt. When it is converted into the $\Delta^{2,6}$-acid by boiling with caustic soda solution, or into the cis-$\Delta^{3,5}$-acid by heating with Ac_2O, the optical activity disappears, the resulting acids containing no asymmetric carbon atom (*Neville*, J. **89**, 1744). — cis-**$\Delta^{3,5}$-Dihydro-o-phthalic acid,** m.p. 174°, *anhydride* m.p. 99°, is formed when the trans $\Delta^{3,5}$-acid is treated with Ac_2O.

Dihydro-terephthalic acids. There are four possible structural isomers, which differ in the position of the double bonds. One of these, the $\Delta^{2,5}$-acid, should exist in two stereoisomeric forms. All the modifications are known; they all melt indistinctly at a high temperature with decomposition.

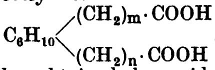
$\Delta^{1,3}$-Dihydro-terephthalic acid, , is obtained by heating α,α'-dibromo-hexahydro-terephthalic acid or Δ^{2}-tetrahydro-terephthalic acid dibromide with alcoholic potash (*Baeyer*, Ann. **258**, 23). *Dimethyl ester,* m.p. 85°.

$\Delta^{1,4}$-Dihydro-terephthalic acid, , is formed by reducing terephthalic acid with sodium amalgam, by boiling the isomeric dihydro-terephthalic acids with sodium hydroxide (id. Ann. **251**, 272), and by reducing p-dichloro-$\Delta^{1,4}$-dihydro-terephthalic acid, obtained by the action of PCl_5 on succino-succinic ester, with sodium amalgam (*Levy*, Ber. **22**, 2122). The *dimethyl ester,* m.p. 130°, contains reactive CH_2-groups and condenses with oxalic ester and with benzaldehyde in presence of NaOEt to give derivatives of terephthalic acid: *phthalide-dicarboxylic acid,* the lactone of the acid $(HOOC)_2C_6H_3CH(OH)COOH$, and *benzyl-terephthalic acid* $(HOOC)_2C_6H_3CH_2Ph$.

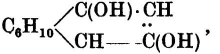
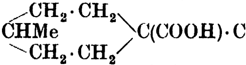
$\Delta^{1,5}$-Dihydro-terephthalic acid, , results from boiling trans $\Delta^{2,5}$-dihydro-terephthalic acid with NaOH; the dimethylester resinifies on exposure to the air (*Baeyer*, Ann. **258**, 18).

$\Delta^{2,5}$-Dihydro-terephthalic acids, , cis and trans, are both formed in the reduction of terephthalic acid. The trans *diphenyl ester* melts at 146°, and the *dimethyl ester* at 77° (id. Ann. **251**, 295). This ester breaks up into terephthalic and hexahydro-terephthalic esters when heated in a CO_2 atmosphere in presence of palladium black.

For the conversion of hexa-, tetra- and di-hydro-terephthalic acids into terpene homologues by means of alkyl-Mg-iodides see *Bogert*, Am. **41**, 1676.

(b) Aliphatic Cyclohexane dicarboxylic Acids. — This name is used for those hydroaromatic dicarboxylic acids in which one or both carboxyl groups are not directly attached to the cyclohexane nucleus. Those of the general formula  $C_6H_{10}\left\langle\begin{matrix}(CH_2)_m\cdot COOH\\(CH_2)_n\cdot COOH\end{matrix}\right.$, in which m = 0, 1, 2 ..., and n = 1, 2, 3... can be obtained by oxidation of suitable hydrogenated ring systems, such as octahydronaphthalene, decahydro-β-naphthol, β-hydrindanone, and the like (*W. Huckel*, Ber. **58**, 447; Ann. **451**, 132).

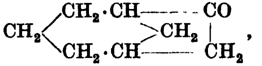
Cyclohexyl-malonic ethyl ester, $C_6H_{11}.CH(CO_2Et)_2$, b.p. 164°/20 mm., and **cyclohexyl-cyanacetic ester,** b.p. 158°/23 mm., are obtained from bromo- and iodocyclohexane with ethyl sodio-malonate and cyanacetate respectively (*Hiers, Adams*, Am. **48**, 2385: *Vogel*, J. **1928**, 2023). **Cyclohexyl-malonic acid,** m.p. 177°, breaks up, on heating, into CO_2 and hexahydro-phenyl-acetic acid (*Freundler*, C. r. **141**, 593). **Hexahydrobenzyl-malonic ester,** $C_6H_{11}\cdot CH_2\cdot CH(CO_2Et)_2$, b.p. 135–136°/3 mm. — For homologues of cyclohexyl-malonic acids, $C_6H_{11}\cdot(CH_2)_nCH(COOH)_2$, where n lies between 1 and 6, see *Hiers* and *Adams*, ibid.

1-Carboxy-cyclohexane-1-acetic acid, m.p. 132–133°, is obtained from the enolised ketone  $C_6H_{10}\left\langle\begin{matrix}C(OH)\cdot CH\\ \cdot\cdot\\ CH{-}{-}C(OH)\end{matrix}\right.$, with alkaline bromine solution (*Ingold, Seeley, Thorpe* J. **123**, 853). For 2- and 3-methylcyclohexane-1-carboxylic-1-acetic acids see *Hunter* et al., J. **1936**, 416. **1-Carboxy-4-methyl-cyclohexane-1-acetic acid,**  $CHMe\left\langle\begin{matrix}CH_2\cdot CH_2\\CH_2\cdot CH_2\end{matrix}\right\rangle C(COOH)\cdot CH_2\cdot COOH$, has been prepared from 4-methylcyclohexanone and ethyl cyanoacetate through ethyl methylcyclohexylidene-cyanoacetate with KCN and with subsequent hydrolysis by HCl and by the oxidation of α-keto-4-methyl-cyclohexane-1,1-diacetic acid (*Desai*, J. **1932**, 1058). Claims have been made that this acid exists in four isomeric forms instead of the two (cis and trans) which would be expected. These claims have not been supported by later work (*Goldschmidt* and *Gräfinger*, Ber. **68**, 279; *Hunter* et al., J. **1936**, 416).

1-Carboxy-cyclohexane-2-acetic acid, *hexahydro-*o-*homophthalic acid*, is obtained from homo-o-phthalic acid (vol. III) by catalytic reduction and from cis and trans β-hydrindanone (p. 169) by oxidation; cis m.p. 146°, trans m.p. 157° (*W. Huckel*, Ann. **451**, 159). *Anhydride*, m.p. 83°. The trans acid is also formed from ethyl $\varDelta^1$-tetrahydrobenzoate and ethyl sodiomalonate (*Boorman* and *Linstead*, J. **1935**, 258). **1-Carboxy-cyclohexane-2-propionic acid,** cis m.p. 103°, trans m.p. 143°, are both obtained from hydrocinnamic-o-carboxylic acid and from cis- or trans-β-decalone. On heating with Ac_2O, both modifications pass into α-hydrindanone (p. 169). **1-Carboxy-cyclohexane-2-butyric acid,** cis form 92–94°, is obtained from tetralone or from phenylene-1-carboxylic-2-butyric acid, and is converted into the trans form m.p. 92–94° when heated with HCl at 200°; both forms give trans α-decalone (*W. Huckel*, Ann. **441**, 13, 37; *Windaus, W. Hückel*, Ber. **56**, 95; **57**, 1285).

Cyclohexane-1,1-diacetic acid, m.p. 181°, has been prepared by hydrolysis with H_2SO_4 of the adduct of one molecule $\varDelta^1$-cyclohexenyl-acetonitrile and two molecules of Na-cyano-acetamide (*Birch, Kon*, J. **123**, 2440).

Cyclohexane-1,2-diacetic acid, cis m.p. 163°, *anhydride* m.p. 52°, is prepared by catalytic reduction of o-phenylene-diacetic acid, or by oxidising cis β-decalol or cis $\varDelta^2$-octalene with $KMnO_4$. The trans form, m.p. 167°, *anhydride* m.p. 79°, is obtained in a similar way from the corresponding trans compounds, and has been resolved into its optical antimers, m.p. 148–150° (*W. Huckel*, Ann. **451**, 140). **Cyclohexane-1-acetic-2-propionic acid,** cis m.p. 109°, trans m.p. 116°, obtained from o-phenylene-acetic-propionic acid or from decalone-carboxylic acid, forms cis or trans β-decalone by ring closure. The cis ester gives cis *decahydro-isoquinoline* (vol. IV) viâ the diazide and diamine (*W. Hückel* and *Goth*, Ber. **58**, 449). **1-Carboxy-cyclohexane-3-acetic acid,** *hexahydro-homoisophthalic acid,* $C_6H_{10}[1,3](COOH)(CH_2COOH)$, m.p. 158°, is obtained from homo-isophthalic acid by reduction; distillation of its calcium salt gives a bicyclic ketone, bicyclo-[1,2,3]-octanone-2 (p. 194)

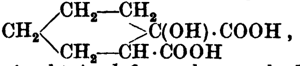


(*Komppa*, et al., Ber. **36**, 3610; Ann. **521**, 242).

Δ^1-Cyclohexenyl-1,2-diacetic acid, m.p. 122°. Its diethyl ester has been prepared by *Baker* (J. **127**, 985) from Δ^1-cyclohexenyl-1-acetic ester which was first combined with Br_2, then condensed with ethyl Na-malonate. The resulting ethyl Δ^1-cyclohexenyl-1-acetic-2-malonate was hydrolysed and the free acid heated to remove CO_2.

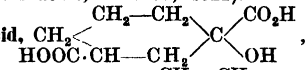
(c) and (d) Hydroxy- and Keto-cyclohexane-dicarboxylic Acids.

α-Hydroxy-hexahydro-phthalic acid,



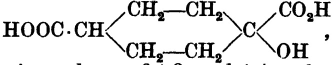
m.p. 130°, a mixture of two stereoisomers, is obtained from the cyanhydrin of 1-cyclohexanone-2-carboxylic acid (*W. Huckel*, Ber. **67**, 1811).

α-Hydroxy-hexahydro-isophthalic acid,



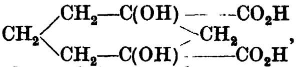
, and

α-Hydroxy-hexahydro-terephthalic acid,



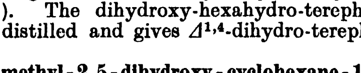
cis m.p. 169°, trans m.p. 229°, are hydrolysis products of 1,3- and 1,4-cyclohexanone carboxylic cyanhydrins (p. 138) (*Baeyer*, Ber. **22**, 2186; *Perkin*, J. **85**, 421).

α,α′-Dihydroxy-hexahydro-isophthalic acid,



m.p. 217° decomp., *anhydride* m.p. 175°, is obtained from its dinitrile, the adduct of hydrocyanic acid and dihydro-resorcinol (p. 112) (*Merling*, Ann. **278**, 49).

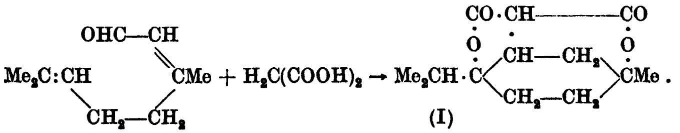
α,α′-Dihydroxy-hexahydro-terephthalic acid,



m.p. 122°, is obtained by hydrolysing with HCl the *dinitrile*, m.p. 180° decomp., formed by the addition of HCN to cyclohexane-1,4-dione (p. 112) (*Zelinsky*, Ber. **40**, 2890).

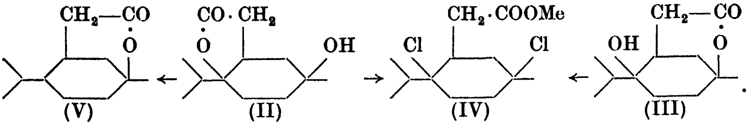
2,5-Dihydroxy-hexahydro-terephthalic acid, $C_6H_8(OH)_2(COOH)_2$, *ethyl ester* m.p. 136°, is formed in the reduction of succino-succinic ester (p. 146) with Na-amalgam, together with 2,5-dihydroxy-tetrahydro-terephthalic ester (b.p. 219°/14 mm.). The dihydroxy-hexahydro-terephthalic ester partly loses water when distilled and gives $\Delta^{1,4}$-dihydro-terephthalic ester (*Stollé*, Ber. **33**, 390).

2-Isopropyl-5-methyl-2,5-dihydroxy-cyclohexane-1-malonic dilactone, *menthane-3-malonic-1,4-dilactone,* the so-called *citrylidene-malonic acid,* (I), $C_{13}H_{18}O_4$, m.p. 186°, is formed from citral and malonic acid in presence of pyridine or piperidine according to the following scheme:

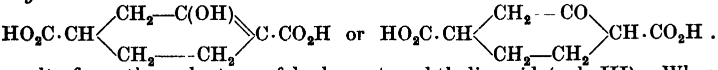


(I)

Alkalis decompose this acid with the formation of two isomeric hydroxy-lactones $C_{12}H_{20}O_3$, (II) m.p. 123·5° and (III) m.p. 118°, and loss of CO_2. These react with HCl in MeOH to give the same dichloro-methyl-ester (IV), which proves their constitution. (II) can be transformed by dehydration and hydrogenation into menthane-acetic-3-lactone-1 (V) (*Kuhn*, Ber. **64**, 1243):



Δ^1-Tetrahydro-2-hydroxy-terephthalic acid, *cyclohexane-2-one-1,4-dicarboxylic acid*

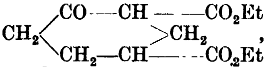


$$\mathrm{HO_2C\cdot CH}\left\langle\begin{array}{l}\mathrm{CH_2{-}C(OH)}\\ \mathrm{CH_2{-}CH_2}\end{array}\right\rangle\mathrm{C\cdot CO_2H} \quad \text{or} \quad \mathrm{HO_2C.CH}\left\langle\begin{array}{l}\mathrm{CH_2{-}CO}\\ \mathrm{CH_2{-}CH_2}\end{array}\right\rangle\mathrm{CH\cdot CO_2H}\,.$$

results from the reduction of hydroxy-terephthalic acid (vol. III). When heated to 60° with water, it loses carbon dioxide and gives cyclohexanone-3-carboxylic acid, the oxime of which is obtained from tetrahydro-hydroxy-terephthalic acid and hydroxylamine chloride (*Baeyer*, Ber. **22**, 2187).

A large number of *keto-tetrahydro-benzene-polycarboxylic esters* and *m-diketo-hexahydro-benzene-carboxylic esters* or *hydroresorcylic esters* have been prepared synthetically from 1,5-diketo- and δ-keto-carboxylic esters, respectively, by the elimination of water or of alcohol. A series of cyclohexanones, dihydro-resorcinols, tetrahydro-benzenes, dihydro-benzenes, etc., has been prepared with these compounds as starting materials (cf. pp. 111, 114). Several alkylidene-bis-acetoacetic esters should be regarded as *cyclohexanol-dicarboxylic esters*.

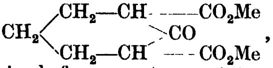
Cyclohexanone-2,4-dicarboxylic ethyl ester,



$$\mathrm{CH_2}\left\langle\begin{array}{l}\mathrm{CO{-}CH{-}CO_2Et}\\ \mathrm{CH_2{-}CH{-}CO_2Et}\end{array}\right\rangle\mathrm{CH_2}\,,$$

b.p. 180°/20 mm., is formed from pentane-α,γ,ε-tricarboxylic ester by internal acetoacetic ester condensation (p. 19; *Kay, Perkin*, J. **89**, 1640).

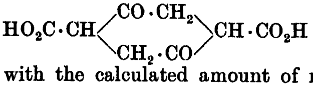
Cyclohexanone-2,6-dicarboxylic methyl ester,



$$\mathrm{CH_2}\left\langle\begin{array}{l}\mathrm{CH_2{-}CH{-}CO_2Me}\\ \mathrm{CH_2{-}CH{-}CO_2Me}\end{array}\right\rangle\mathrm{CO}\,,$$

keto-form m.p. 125°, enol a liquid, is obtained from pentane-ω-tetra-carboxylic ester with NaOEt, followed by hydrolysis and loss of CO_2 (*Meerwein*, unpublished). The *ethyl ester*, b.p. 144°/3 mm., is prepared from trimethylene bromide with Mg and acetone-dicarboxylic ester (*Guha*, Current Sc. **4**, 153). **2-Methyl-cyclohexanone-2,6-dicarboxylic ester,** b.p. 160°/10 mm., see *Kötz*, Ann. **350**, 214.

Succino-succinic acid

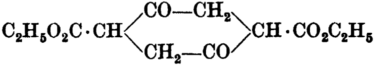


$$\mathrm{HO_2C\cdot CH}\left\langle\begin{array}{l}\mathrm{CO\cdot CH_2}\\ \mathrm{CH_2\cdot CO}\end{array}\right\rangle\mathrm{CH\cdot CO_2H}$$

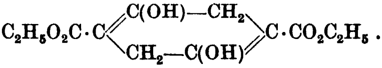
is obtained by hydrolysing its diethyl ester with the calculated amount of normal sodium hydroxide, and by treating 2,5-dihydroxy-terephthalic ester with sodium amalgam. The dry acid breaks down into two molecules of carbon dioxide and cyclohexane-1,4-dione (p. 112) when heated to 200° (*Baeyer*, Ber. **22**, 2168).

Succino-succinic diethyl ester, m.p. 126° (*dimethyl ester* m.p. 152°) is produced by the action of K, Na, NaOEt, K-acetate, NH_3, or Me_2NH upon succinic ester, or upon γ-chloro- or γ-bromo-acetoacetic ester (*Herrmann*, Ann. **211**, 306; *Mewes*, ib. **245**, 74) and also by the action of silver cyanide on iodo-acetoacetic ester (*Schonbrodt*, Ann. **258**, 182) and by the reduction of 2,5-dihydroxy-terephthalic ester with zinc and HCl (*Baeyer*, Ber. **19**, 432; *Sommelet*, Bull. **29** (1921), 402). Its preparation from succinic alkyl esters is improved by adding the corresponding acetic ester (*Liebermann*, Ann. **404**, 272).

Succino-succinic ester behaves very much like phloroglucinol. It shows many of the reactions of a ketone, as if it had this structure and were cyclohexadione-2,5-carboxylic ester (I), but on the other hand it also behaves as a phenol, as if it were 2,5-dihydroxy-dihydro-terephthalic ester (II) (*Baeyer*, Ber. **24**, 2692)

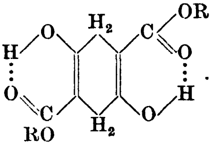
I. 

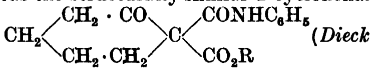
$$C_2H_5O_2C\cdot CH\left\langle\begin{matrix}CO-CH_2\\CH_2-CO\end{matrix}\right\rangle CH\cdot CO_2C_2H_5$$

II. 

$$C_2H_5O_2C\cdot C\left\langle\begin{matrix}C(OH)-CH_2\\CH_2-C(OH)\end{matrix}\right\rangle C\cdot CO_2C_2H_5\,.$$

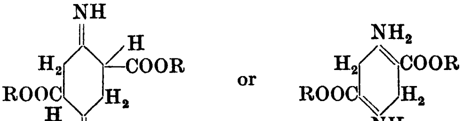
To account for its extraordinary stability *Hantzsch* (Ber. **48**, 772) suggested that its formula should be written as that of a "rigid cis-dienol", a 1,4-dihydro-dihydroxy-terephthalic ester, the hydroxyl and ester groups entering into hydrogen-bond formation:



The ester crystallises in pale-green triclinic prisms or colourless needles. It is insoluble in water, dissolves with difficulty in ether and very readily in alcohol; the solution shows a bright blue fluorescence, and is coloured cherry red by $FeCl_3$. It dissolves in alkalies with a yellow colour, two hydrogen atoms being replaced by the alkali metal. It does not combine with phenyl isocyanate, whereas the structurally similar 2-cyclohexanone-carboxylic ester does so and forms  (*Dieckmann*, Ann. **317**, 104).

$$CH_2\left\langle\begin{matrix}CH_2\cdot CO\\CH_2\cdot CH_2\end{matrix}\right\rangle C\left\langle\begin{matrix}CONHC_6H_5\\CO_2R\end{matrix}\right.$$

Succino-succinic ester gives with NH_3 a compound (III) which crystallises in white needles m.p. 178° (*Kauffmann*, Ber. **48**, 1267; *Bogert*, Am. **27**, 1127):



(III)

Its reactions with primary amines have been studied by *Liebermann*, Ann. **404**, 272.

With hydroxylamine (in alkaline or acid solution) succino-succinic ester is oxidised with loss of CO_2 and yields **quinone-dioxime-carboxylic ester** $C_6H_3(NOH)_2\cdot CO_2Et$, m.p. 174° (*Jaurenaud*, Ber. **22**, 1283).

With phenylhydrazine it forms a phenylhydrazine derivative of dihydroterephthalic acid (*Baeyer*, Ber. **24**, 2687; *Kishner*, ib. **26**, R. 590), while with hydrazine itself it yields *hexahydro-benzo-3,4-dipyrazolone* (vol. IV) (*Rothenburg*, Ber. **27**, 472). See also dichloro-dihydro-terephthalic acid p. 143.

If sodio-succino-succinic diethyl ester is treated with alkyl iodides, it yields the following compounds:

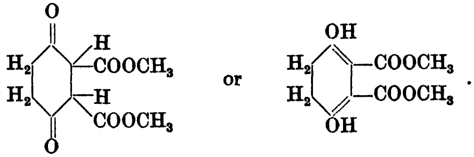
Diethyl-succino-succinic ester: *cis*, a liquid; *trans*, m.p. 65°.

Di-n-propyl-succino-succinic ester: *cis*, a liquid; *trans*, m.p. 86°.

Di-isopropyl-succino-succinic ester: *cis*, a liquid; *trans*, m.p. 116°.

Methyl-n- and **methyl-isopropyl-succino-succinic ester** b.p. of both, 195–200°/25 mm.

Cyclohexane-1,4-dione-2,3-dicarboxylic methyl ester m.p. 55–57° is a 1,2 isomer of succino-succinic ester, prepared from quinone + HCN, by hydrolysing, esterifying and reducing the 3,6-dihydroxy-phthalic ester obtained (*Helferich*, Ber. **54**, 155):



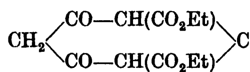
p-Dichloro-quinone-dicarboxylic ester $C_6O_2Cl_2(CO_2Et)_2$ m.p. 195° forms greenish-yellow crystals (*Boniger*, Ber. **21**, 1761). On reduction with zinc dust and AcOH it is converted into:

p-Dichloro-quinol-dicarboxylic ester $C_6H_2O_2Cl_2(CO_2Et)_2$, which crystallises in two different forms—colourless needles and yellow-green plates (*Hantzsch*, Ber. **20**, 2796; *Boniger*, Ber. **21**, 1759; *Goldschmidt*, ib. **23**, 260). A similar behaviour is shown by dibromo- and di-iodo-quinol-dicarboxylic esters (*Guinchard*, Ber. **32**, 1742): see also the two forms of 2,5-dihydroxy-terephthalic ester (vol. III).

p-Dihydroxy-quinone-dicarboxylic ester $C_6O_2(OH)_2(CO_2Et)_2$, m.p. 151°, can be prepared by shaking dichloro-quinol-dicarboxylic ester with sodium hydroxide, and by the action of nitrous acid upon dihydroxy-terephthalic ester (*Loewy*, Ber. **19**, 2385). It crystallises in pale-yellow leaflets and intensely greenish-yellow prisms (*Hantzsch*, Ber. **20**, 1307). It has an acid reaction and forms salts with two equivalents of the metals. It does not form a dioxime with hydroxylamine, but a hydroxylamine salt, and with phenylhydrazine a phenylhydrazine salt (*Boniger*, Ber. **22**, 1290). Furthermore, it does not react with phenyl isocyanate (*Guinchard*, Ber. **23**, 265). Boiling hydrochloric acid decomposes the ester into carbon dioxide and dihydroxy-quinone. When reduced with SO_2, the ester takes up two H-atoms and gives:

Tetrahydroxy-terephthalic ester $C_6(OH)_4(CO_2Et_2)$, or **dihydroxy-dihydroquinone-carboxylic ester** $C_6H_2(O_2)(OH)_2(CO_2Et)_2$, which crystallises in golden-yellow leaflets, m.p. 178° (*Hantzsch*, Ber. **20**, 2798). Its alkaline solution is oxidised on exposure to the air (giving up two hydrogen atoms) to dihydroxy-quinone-dicarboxylic ester, and it gives therefore the same products with hydroxylamine and phenylhydrazine (*Boniger*, Ber. **22**, 1291). It forms a tetracarbanilido derivative (*Goldschmidt*, Ber. **23**, 267) with four molecules of phenyl isocyanate.

Phloroglucinol-dicarboxylic ester

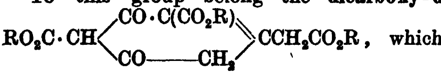


$$CH_2\begin{matrix}\diagup CO-CH(CO_2Et)\diagdown \\ \diagdown CO-CH(CO_2Et)\diagup\end{matrix}CO$$

, m.p. 104°, is formed by the condensation of three molecules sodio-malonic acid ester by heating to 120–145°, when EtOH and CO_2 are eliminated; acetone tricarboxylic ester is an intermediate product; it is also formed by condensation of acetone-dicarboxylic ester and malonic ester with NaOEt (*Rimini*, Gazz. **26**, II, 374; *Leuchs*, Ber. **41**, 4171). It behaves like succino-succinic ester, dissolving without change in alkalies, and gives a cherry-red colour with ferric chloride. With acetic anhydride it forms a triacetyl derivative, with hydroxylamine a trioxime (*Bally*, Ber. **21**, 1766), and with phenyl isocyanate a tricarbanilido-derivative (*Dieckmann*, Ber. **37**, 4637). When fused with caustic potash it gives phloroglucinol.

(C) Cyclohexane-tricarboxylic Acids

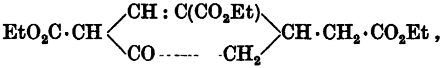
To this group belong the **dicarboxy-dihydroxyphenyl-acetic esters**



$$RO_2C\cdot CH\begin{matrix}\diagup CO\cdot C(CO_2R)\diagdown \\ \diagdown CO\text{———}CH_2\diagup\end{matrix}CCH_2CO_2R$$

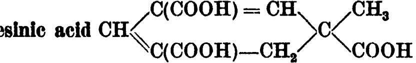
, which are condensation products

of acetone-dicarboxylic ester (*Dootson*, J. 77, 1196), and the analogous **dicarboxy-dihydro-hydroxy-phenylacetic ester**



$$EtO_2C\cdot CH\left\langle\begin{array}{l}CH:C(CO_2Et)\\CO\text{------}CH_2\end{array}\right\rangle CH\cdot CH_2\cdot CO_2Et,$$

m.p. 82°, obtained by condensing glutaconic ester by means of sodium ethoxide free from alcohol (*v. Pechmann*, Ber. 37, 2113).

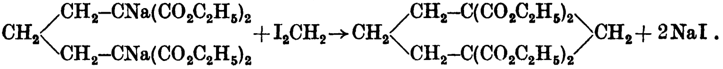
Methyl-dihydro-trimesinic acid  is formed

$$CH\left\langle\begin{array}{l}C(COOH)=CH\\C(COOH)-CH_2\end{array}\right\rangle C\left\langle\begin{array}{l}CH_3\\COOH\end{array}\right.$$

from pyruvic acid by heating with sodium hydroxide. The acid is the intermediate product of the synthesis of uvitic acid from pyruvic acid. On heating with concentrated sulphuric acid it splits off CO_2 and 2 H, and passes smoothly into uvitic acid; on melting it gives, together with uvitic acid, *dihydro-uvitic acid* $C_6H_5(CH_3)(COOH)_2$, m.p. 236°, and several *tetrahydro-uvitic acids*. When it is reduced with Na amalgam **methyl-tetrahydro-trimesinic acid** $C_6H_6(CH_3)(COOH)_3$, m.p. 221° decomp. is formed (*Wolff*, Ann. 305, 125).

(D) Cyclohexane-tetracarboxylic Acids

Acids with two carboxyl groups attached to the same carbon atom have been obtained synthetically by the action of trimethylene bromide upon the disodium compound of methylene-dimalonic ester, and also by the action of methylene iodide on disodio-trimethylene-dimalonic ester: cyclohexane 1,1,3,3-tetracarboxylic ester is obtained from n-butane-tetracarboxylic ester with ethylene bromide (*Perkin jun.*):



$$CH_2\left\langle\begin{array}{l}CH_2-CNa(CO_2C_2H_5)_2\\CH_2-CNa(CO_2C_2H_5)_2\end{array}\right. + I_2CH_2 \rightarrow CH_2\left\langle\begin{array}{l}CH_2-C(CO_2C_2H_5)_2\\CH_2-C(CO_2C_2H_5)_2\end{array}\right\rangle CH_2 + 2NaI.$$

For cyclohexane-1,1,4,4-tetracarboxylic ester (*Perkin*) see pages 20 and 141.

1,1,3,3-Cyclohexane-tetracarboxylic acid loses CO_2 at 220° and decomposes into a mixture of cis and trans hexahydro-isophthalic acids (*Perkin*, J. 59, 798, 990).

1,2,3,4-Cyclohexane-tetracarboxylic acid, *hexahydro-mellophanic acid*, m.p. (with 1 mol. H_2O) *ca.* 168°, is obtained from the condensation product of mucic ester and maleic anhydride by hydrogenation and hydrolysis (*Farmer, Warren*, J. 1929, 897).

(E) Cyclohexane-hexacarboxylic Acids

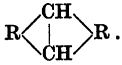
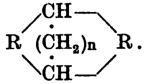
The two forms of **cyclohexane-1,2,3,4,5,6-hexacarboxylic acid** or *hydromellitic acid* $C_6H_6(COOH)_6$ belong to this group. When an ammoniacal solution of benzene-hexacarboxylic acid, mellitic acid (vol. III), is treated with sodium amalgam, an unstable hexahydro-acid is obtained as a syrup which crystallises indistinctly. This acid, when heated in a sealed tube with conc. HCl at 180°, is converted into the stable **iso-hydromellitic acid**, which crystallises in prisms. Both acids decompose on heating. From the Ag salt of iso-mellitic acid a *Me-ester* has been prepared by means of MeI, m.p. 125° (*Baeyer*, Ann. Suppl. 7, 15).

II. POLYNUCLEAR ALICYCLIC COMPOUNDS

BY ADOLF BUTENANDT AND KARL NIEDERLÄNDER

This class comprises:

1. **Compounds in which the rings are united directly: R>CH—CH<R and those in which a chain separates the rings: R>CH·[CH$_2$]$_n$·CH<R**

2. **Spiranes,** in which one carbon is common to two rings: $R{>}C{<}R$
3. **Condensed Ring Systems** in which two ring members are common to both rings:  $R\left\langle\begin{matrix}CH\\|\\CH\end{matrix}\right\rangle R$.
4. **Bridged Ring Systems,** also called meso- or endo-methylene, meso- or endo-ethylene etc., compounds, in which two carbocyclic systems share three, or in some cases more than three carbon atoms:  $R\begin{matrix}CH\\(CH_2)_n\\CH\end{matrix}R$.

While the spiranes are exclusively synthetic products, representatives of the first class (see Carotenoids), of condensed ring systems and of endo-methylene compounds are frequently met with in nature (see Terpenes, and Naturally Occurring Substances).

1. RINGS DIRECTLY UNITED OR SEPARATED BY A CHAIN

Apart from one representative of the dicyclopentyl series which is found in petroleum, members of this class of compounds have only been met among the fat-soluble polyene dyes (lipochromes), which contain an unsaturated hydrocarbon chain carrying at each end a ring of the ionone type.

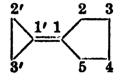
Synthetically these polynuclear compounds are obtained by the following general methods:

1. Application of *Wurtz*'s method (*Meiser*, Ber. **32**, 2054; *Zelinsky*, ib. **66**, 1422).
2. Reduction of cyclic ketones to pinacols, followed by elimination of water and hydrogenation, gives compounds in which the rings are directly united (*Zelinsky*, Ber. **62**, 2180); *Godchot*, C. r. **186**, 767; *Ruzicka*, Helv. **14**, 1319).
3. Internal condensation of the same ketones by means of $NaOC_2H_5$, CaH_2 (*Wallach*, Ann. **389**, 169; *Taboury*, C. r. **169**, 62; *Godchot*, ib. **174**, 618).
4. The reaction between cyclanones and *Grignard* compounds of cyclic halides (*Bedos*, Bull. **39** (1926), 473).
5. Dicyclohexyl compounds, in particular, are obtained by the catalytic reduction of the corresponding aromatic derivatives (diphenyl, diphenyl-methane etc.)

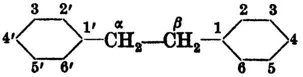
For alterations in the carbon skeletons, which sometimes take place in the course of chemical reactions (pinacolin transformation, reduction with HI and P etc.), see ring transitions p. 11.

The methods for determining the constitution, the chief reactions, and the physiological action of carotenoids, are discussed in the section dealing with Natural Colouring Matters p. 407.

The conventions used in the nomenclature and the numbering of the carbon atoms will be found in *Richter-Stelzner* vol. III, 1914/1915, e.g.



Cyclopropylidene-cyclopentane



α, β-Dicyclohexyl-ethane

DICYCLOPROPANE DERIVATIVES

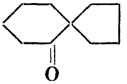
Cyclopropyl-cyclopropane-2,2,3–2′,2′,3′-hexacarboxylic acid $C_{12}H_{10}O_{12}$ m.p. 197°, decomposes at the melting point into the 2,3–2′,3′ **tetracarboxylic acid** $C_{10}H_{10}O_6$ m.p. 105–107°. The *methyl ester*, m.p. 148°, of the first acid is formed from α, α′-dichloro-muconic ester with Na-malonic ester (*Farmer*, J. **123**, 3332).

DICYCLOPENTANE DERIVATIVES

Dicyclopentyl, $C_5H_9—C_5H_9$, b.p. 188–189·5°/744 mm., is obtained from cyclopentyl bromide with Na (*Meiser*, Ber. **32**, 2054) or from cyclopentyl-cyclopentanone hydrazone with KOH (*Zelinsky*, C. 1931 I 1098).

3,3′-Dimethyl-dicyclopentyl, b.p. 213–214° occurs in petroleum and is formed when carbazole (vol. IV) is treated with HI and P, possibly with intermediate formation of dicyclohexyl (*Schmidt*, Ber. **45**, 1779).

Cyclopentyl-cyclopentanol-2, $C_{10}H_{18}O$, cis form m.p. 28°, b.p. 235–236°, *phenylurethane* m.p. 88–89°, trans compound b.p. 117–118°/12 mm., is obtained from 2-cyclopentyl- or 2-cyclopentylidene-cyclopentanone, and also as a by-product in the reduction of cyclopentanone (p. 55) (*Wallach*, Ann. **389**, 169; *Godchot*, C. r. **153**, 1010; *Zelinsky*, Ber. **62**, 2180; C. 1931 I 1098). The trans form is converted into $\Delta^{9,10}$-octalin (p. 173) by treatment with $ZnCl_2$ at 140°; the cis form yields, in addition, a small amount of a hydrocarbon presumably identical with cyclopentyl-cyclopentene-1 (*nitrosochloride* m.p. 111°) (*Zelinsky*, Ber. **59**, 2580; *Hückel*, Ann. **477**, 131).

1,1′-Dihydroxy-dicyclopentyl, $C_5H_8(OH)\cdot C_5H_8(OH)$, the pinacol of cyclopentanone, m.p. 107–108°, is obtained from the latter by reduction with Na and moist ether. When the compound is treated with dilute sulphuric acid, the carbon skeleton rearranges with the loss of water and formation of cyclopentane-spiro-cyclohexane-2-one (p. 160)  (*Zelinsky*, Ber. **62**, 2180).

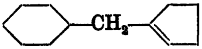
Cyclopentyl-cyclopentanone-2 $C_{10}H_{18}O$, b.p. 232–233°, smells like menthol and is obtained from cyclopentylidene-cyclopentanone (p. 55) by catalytic reduction, or as a by-product in the same treatment of cyclopentanone. On further reduction with Na + alcohol it yields **cyclopentyl-cyclopentanol-2** (cf. above), and on oxidation δ-cyclopentyl-δ-keto-n-valeric acid (*Wallach*, Ann. **389**, 169). **Cyclopentylidene-cyclopentanone-2** $C_{10}H_{14}O$ b.p. 117–119°/12 mm. (*oxime* m.p. 128°) is prepared by auto-condensation of cyclopentanone with $NaOC_2H_5$ or with CaH_2 (*Wallach*, Ber. **29**, 2963; Ann. **389**, 179; *Taboury*, C. r. **169**, 62). When the compound is ethylated with EtI and Na, the semicyclic double bond migrates into the ring, and Δ^1-cyclopentenyl-1-ethyl-cyclopentanone-2 is formed; isopropylidene-cyclopentanone shows a similar behaviour (p. 57) (*Kon*, J. **1926**, 3101).

α, β-**Dicyclopentyl-ethane** $C_{12}H_{22}$, b.p. 206–207°, is prepared by *Wurtz*' method from sodium and cyclopentyl-methyl-iodide, which is available from cyclopentyl-magnesium chloride and trihydroxy-methylene through *cyclopentenyl-methanol*, b.p. 162–163° (*Zelinsky*, Ber. **66**, 1422).

CYCLOPENTYL-CYCLOHEXANE DERIVATIVES

2-Methyl-cyclopentyl-cyclohexane $C_{12}H_{22}$, b.p. 225–227° can be synthesised from methyl-cyclopentanone and cyclohexyl magnesium bromide with the intermediate steps: *1-cyclohexyl-2-methylcyclopentanol* $C_{12}H_{22}O$, b.p. 119°/8 mm. and *2-methyl-cyclopentenyl-cyclohexane* $C_{12}H_{20}$, b.p. 228–230° (*Zelinsky*, C. 1933 II 1673).

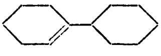
Δ^1-**Cyclopentenyl-cyclohexyl-methane** is formed by eliminating water from trans *cyclohexyl-cyclohexanol-2*, m.p. 52°, by means of $ZnCl_2$. Its

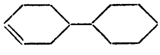


constitution is established by ozonisation and subsequent *Beckmann* rearrangement of the isomeric oximes; this gives glutaric acid and hexahydrobenzylamine from one isomer and amino-butyric acid and cyclohexyl-acetic acid from the other (*Hückel*, Ann. **477**, 106).

DICYCLOHEXANE DERIVATIVES

Dicyclohexyl $C_6H_{11}\cdot C_6H_{11}$, b.p. 227–228° has been prepared: (1) by catalytic hydrogenation of diphenyl, (2) from cyclohexyl-cyclohexanol-2 or -4 and $ZnCl_2$ through the corresponding *dicyclo-hexenes* $C_{12}H_{20}$, (*-1*, b.p. 234° and *-3*, b.p. 237°) and subsequent hydrogenation, (3) from cyclohexyl-cyclohexanol-2 with HI, and (4) from iodo-cyclohexane with sodium (*Wallach*, Ber. **40**, 70; *Schrauth*, Ber. **56**, 1900; *Huckel*, Ann. **477**, 106; *Zelinsky*, C. 1933 II 1674). The position of the double bond in **dicyclohexene-1** has been established by the *Beckmann* rearrangement of the oxime of the ozonisation product; *cyclohexyl amine, adipic acid, hexahydro-benzoic acid* and *δ-amino-valeric acid* are produced (*Huckel*, l. c.).





Cyclohexylidene-cyclohexane $C_{12}H_{20}$, b.p. 236–237°, has been prepared by reducing *cyclohexylidene-cyclohexanone*, the condensation product of cyclohexanone (*Zelinsky*, C. 1933 II 1673).

$\Delta^{1,1'}$**-Di-cyclohexenyl** $C_{12}H_{18}$, b.p. 120–125°/15 mm., is formed from *cyclohexanone-pinacol* with dilute H_2SO_4 (*Wallach*, Ann. **381**, 112).

The **partially hydrogenated diphenyls** in which one benzene ring is intact, and which are systematically related to the dicyclohexane derivatives are discussed in vol. III.

Cyclohexyl-cyclohexanol-2, cis form m.p. 63°, is obtained from cyclohexene oxide and cyclohexyl-Mg chloride (*phenylurethane* m.p. 122°); the trans form, m.p. 52°, can be prepared (1) from cyclohexanol with solid KOH, b.p. 136–138°/13 mm. (*phenylurethane* m.p. 114°), *dicyclohexyl-cyclohexanol* m.p. 124° being a by-product (*Bedos*, Bull. **39** (1926), 473), (2) from o-cyclohexyl-phenol and o-hydroxy-diphenyl by catalytic hydrogenation with PtO_2 (*Hückel*, l. c.), (3) by catalytic reduction of cyclohexylidene-cyclohexanone in the presence of Ni + MgO (Brit. Pat. 397,883).

Cyclohexyl-cyclohexanol-4, cis form m.p. 105°, trans form m.p. 84°, is prepared similarly by reduction of the corresponding aromatic p compounds.

1,1'-Dihydroxy-dicyclohexyl $C_{12}H_{22}O_2$, m.p. 130°, is the pinacol of cyclohexanone, from which it is prepared by reduction with sodium. The isomeric **4,4'-dihydroxy-dicyclohexyl** m.p. 204–207°, has been obtained from 4,4'-dihydroxy-diphenyl with hydrogen and nickel at 200° and 100 atm. pressure (*Zelinsky*, Ber. **34**, 2801; *Waldeland*, Am. **55**, 4234).

Cyclohexylidene-cyclohexanone $C_6H_{10}:C_6H_8O$, b.p. 274–276°, *semicarbazone* m.p. 190°, is the condensation product formed when cyclohexanone is treated with HCl in ether, and is the starting material for a number of derivatives containing this ring system, such as cyclohexyl-cyclohexanol, cyclohexylidene-cyclohexane, dicyclohexene and dicyclohexyl (*Zelinsky*, C. 1933 II 1674).

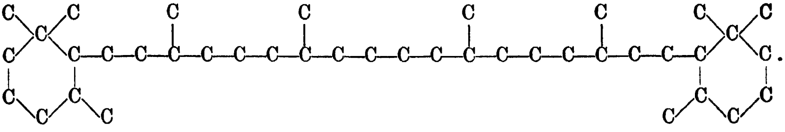
3,3'-Diketo-dicyclohexyls, diketo-perhydro-diphenyls, are obtained from Δ^2-cyclohexenones by reduction with sodium amalgam in acid solution.

Dicarvelone $C_{20}H_{30}O_2$, m.p. 149°, from carvoxime (*Wallach*, Ann. **279**, 379; **305**, 223).

Diethyl dicyclohexyl-2,2'-dicarboxylate $C_{18}H_{30}O_4$, cis form b.p. 155–158°/1–2 mm., trans form m.p. 84–85°, is obtained from diphenic diethyl ester by catalytic reduction with Ni at 200° and 100–160 atm. (*Waldeland*, Am. **55**, 4234).

α, β-2,6,6-Trimethyl-dicyclohexenyl-Δ^1**-ethane,** *di-β-cyclogeranyl* $C_{20}H_{34}$, m.p. 111°, was found to be the product of the attempted preparation of the *Grignard* compound from *β*-cyclogeraniol bromide with Mg in ether (*Kuhn*, Ber. **67**, 357).

Among the representatives of chain-linked dicyclohexanes, several natural carotenoids should be mentioned; these will be treated in detail in the chapter devoted to polyene bodies (p. 407). Up to the present the following compounds have been found in nature: the hydrocarbons α- and *β-carotene* $C_{40}H_{56}$, the polyene alcohols *cryptoxanthin* $C_{40}H_{56}O$, *lutein*, *zeaxanthin* $C_{40}H_{56}O_2$, *flavoxanthin* $C_{40}H_{56}O_3$, *violaxanthin*, *taraxanthin* $C_{40}H_{56}O_4$, *fucoxanthin* $C_{40}H_{56}O_6$ and the diketone *rhodoxanthin* $C_{40}H_{50}O_2$. The carbon frame of those compounds is



DICYCLOHEPTANE DERIVATIVES

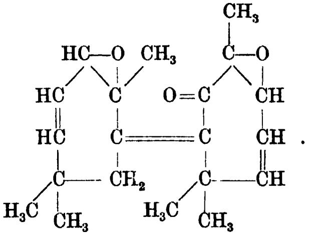
Dicycloheptyl, *disuberyl* $C_7H_{13}\cdot C_7H_{13}$, b.p. 290°, has been made by *Wurtz*' method from cycloheptyl bromide.

$\Delta^{1,1'}$-**Dicycloheptenyl** $C_7H_{11}\cdot C_7H_{11}$, b.p. 149–150°/19 mm., is prepared from the pinacol of suberone (cf. next para.) by boiling with dilute H_2SO_4 or with aqueous oxalic acid, together with a spiro compound (p. 160) (*Godchot*, C. r. **186**, 767).

Cycloheptyl-cycloheptanol, b.p. 158–161°/20 mm., *allophanate*, m.p. 185° from cycloheptylidene-cycloheptanone (cf. below) with Na + alcohol, and **1,1′-dihydroxy-dicycloheptyl**, the pinacol of suberone, m.p. 78°, by reduction of that ketone (*Godchot*, C. r. **174**, 618; **186**, 767).

Cycloheptylidene-cycloheptanone-2, b.p. 143–145°/8 mm., from suberone with CaH_2 (*Godchot*, l. c.).

Eucarvone on autoxidation or if heated with H_2O_2 gives **trimethyl-oxido-cycloheptylidene-trimethyl-oxido-cycloheptenone** $C_{20}H_{26}O_3$, of which two isomeric forms are known, m.p. 215° and m.p. 217°; *semicarbazones*, m.p. 266° and m.p. 254°:



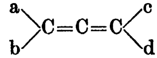
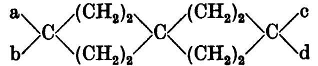
DICYCLO-OCTANE DERIVATIVES

Dicyclo-octyl $C_{16}H_{30}$, b.p. *ca.* 140°, can be obtained by hydrogenation with Pt in acetic acid of $\Delta^{1,1'}$-*dicyclo-octenyl* $C_{16}H_{26}$, m.p. 37°, b.p. 115–116°/0·25 mm., which is prepared from cyclo-octanone pinacol $C_{16}H_{30}O_2$, m.p. 94°, with oxalic acid (*Ruzicka*, Helv. **14**, 1319; *Godchot*, C. r. **185**, 1202).

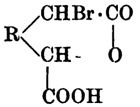
2. SPIRANES

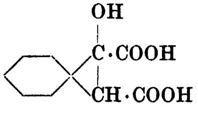
(The name is derived from Latin *spira*, a coil or twist; *Baeyer*, Ber. **33**, 3771.)

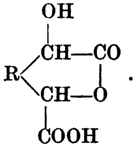
The smallest bicyclic system of this kind is allene $H_2C{=}C{=}CH_2$, which has been described among the olefins (I, 114). Increasing the number of ring members one arrives first at the methylene-cycloparaffin series, $R>C{=}CH_2$, rings with a semicyclic double linkage, the representatives of which have been described under the various ring systems. Finally, one arrives at the spiranes R > C < R.

Molecular Asymmetry of Spiranes. Spiro compounds which correspond to the allene type  $\overset{a}{\underset{b}{>}}C=C=C\overset{c}{\underset{d}{<}}$, and in fact all compounds of the general formula  $\overset{a}{\underset{b}{>}}C\overset{(CH_2)_2}{\underset{(CH_2)_2}{<>}}C\overset{(CH_2)_2}{\underset{(CH_2)_2}{<>}}C\overset{c}{\underset{d}{<}}$ are asymmetric in structure, since they have neither a centre nor a plane of symmetry. Hence they can be resolved into optically active components. The same is true for compounds of the above formula where c = a and d = b, and compounds of this type have been resolved (see *Mills* and *Noddak*, J. **117**, 1407; **119**, 2097; *Kohler*, *Walker* and *Tischler*, Am. **57**, 1743; *Maitland* and *Mills*, J. **1936**, 987).

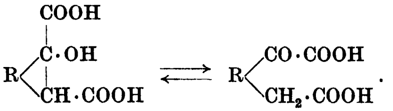
The cyclopropane-spiro-cyclohexane system is distinguished, from the other spirane systems, by its ease of formation and stability. The bromolactone I of a 6-membered ring yields with alkali almost nothing but the cyclopropane-spiro-cyclohexane compound II, while with the corresponding 5- and 7-membered ring derivatives the formation of the hydroxylactonic acid III predominates:


I

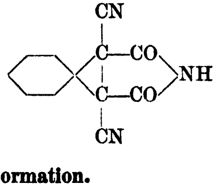

II


III

The equilibrium between spirocyclic hydroxy-cyclopropane-1,2-dicarboxylic acids and corresponding α-keto-glutaric acids lies very much on the side of the spirane compound when R is a six-membered ring:

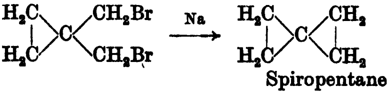


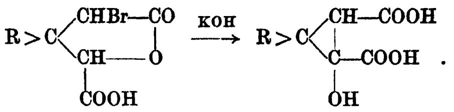
Cyclohexane-spiro-cyclopropane-1,2-dicarboxylic acid resists the action of concentrated HCl, but the spirane compounds of the 5- and 7-rings are disrupted. The same is true of the resistance to alkali of cyclohexane-spirocyclopropane-dicyano-dicarboxylic imide:



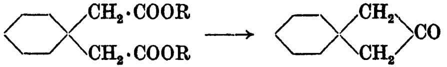
General Methods of Formation.

(1) Spirocyclic compounds can be obtained by *Wurtz*' reaction from cyclic dihalogen derivatives and also from cyclic halogenated fatty acids, cyclic α-bromolactonic esters, etc. as in the syntheses of cycloparaffins:

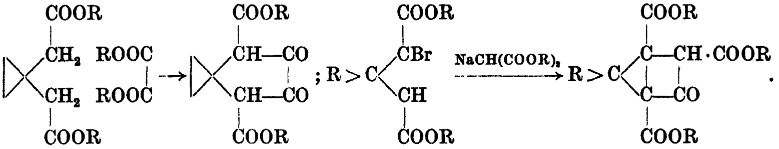

Spiropentane



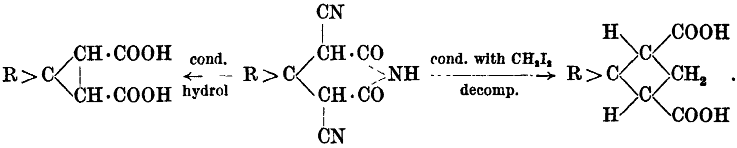
(2) Internal condensations of esters by *Dieckmann's* method, and condensations with oxalic, malonic, succinic. etc. esters can also be used:



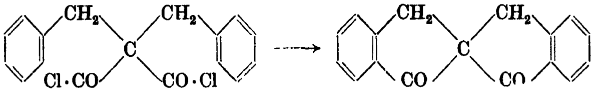
Cyclohexane-spiro-cyclobutanone



(3) Cyclanones react with cyanacetic ester forming cyclic dicyanodicarboxylic imides which are converted by ring closure into spirocyclane derivatives, according to the scheme:

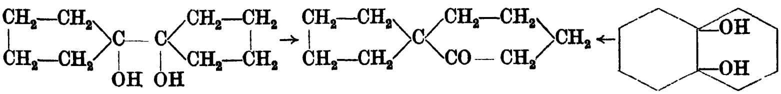


(4) Condensation of cyclic acid chlorides by $AlCl_3$, quinoline etc. can be used in isolated cases:

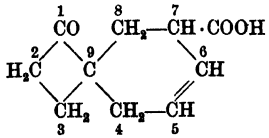


Bis-hydrindone-spirane.

(5) A special method which should be noticed consists of the pinacolin transformation of cyclic pinacols. Both 9,10-octalin-diol and the pinacol resulting from cyclopentanone yield cyclopentane-spirocyclohexanone under the influence of acids:



The position of substituents in spirane compounds can be indicated in a rational system by numbering consecutively the carbon atoms to which substituents can be attached, beginning with the smaller ring, e.g.

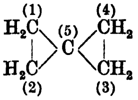


Cyclobutane-1-one-spiro-Δ^5-cyclohexene-7-carboxylic acid or spiro-[3, 5]-Δ^5-nonene-1-one-7-carboxylic acid

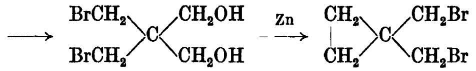
The square brackets indicate the number of ring-members united to the spiro carbon atom.

THE SPIRO-[2,2]-PENTANE SYSTEM

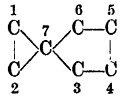
The simplest representative of the spirane class, **spiro-[2,2]-pentane**



(spiro-dicyclopropane) C_5H_8, b.p. 40°, has been prepared from pent-erythritol-tetrabromohydrin by heating with Zn and EtOH (*Gustavson*, J. pr. **54**, 97; C. r. **123**, 242; *Fecht*, Ber. **40**, 3884. The synthesis in steps from penterythritol through the dibromides

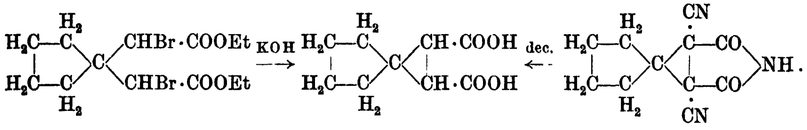


establishes its constitution beyond doubt (*Zelinsky*, Ber. **46**, 160). On oxidation with permanganate the hydrocarbon gives a cyclic glycol $C_5H_8(OH)_2$. A *dibromide* $C_5H_8Br_2$ is also known and a *ψ-nitrosite* $C_5H_8O_3N_2$, m.p. 145°, which is colourless at ordinary temperature, but deep blue when molten or in solution. The spiro-[2,2]-pentane ring is opened by KCN and hydrolysis gives *cyclopropane-1-carboxylic-1,β-propionic acid* $C_7H_{10}O_4$, m.p. 162°.



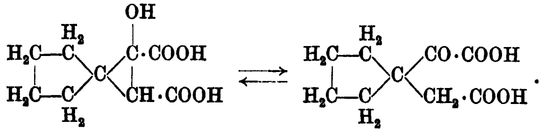
THE SPIRO-[2,4]-HEPTANE SYSTEM

Cyclopentane-spiro-cyclopropane-1,2-dicarboxylic acid, $C_9H_{12}O_4$, trans form m.p. 211° (*dianilide* m.p. 289°) is obtained from ethyl α,α′-dibromo-cyclopentane-1,1-diacetate with KOH + EtOH, and from cyclopentanone by the cyanacetic ester method:

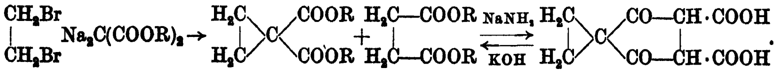


The cis form, m.p. 170° (*anilic acid* m.p. 191—192°) can be obtained through the non-crystalline anhydride of the trans acid (*Becker, Birch, Thorpe*, J. **117**, 1579; **121**, 1821).

Cyclopentane-spiro-1-hydroxycyclopropane-1,2-dicarboxylic acid, cis form, m.p. 163°, is obtained from cyclopentane-1,1-α,α-dibromo-diacetic acid by ring closure with K_2CO_3 in MeOH. In solution the acid reaches equilibrium with the corresponding monocyclic ketonic acid, m.p. 112° (*Lanfear, Thorpe*, J. **123**, 1683):

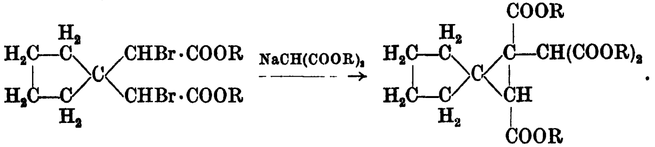


Cyclopropane-spiro-cyclopentane-3,6-dione-4,5-dicarboxylic acid $C_9H_8O_6$, m.p. 161°, has been made by the following steps:

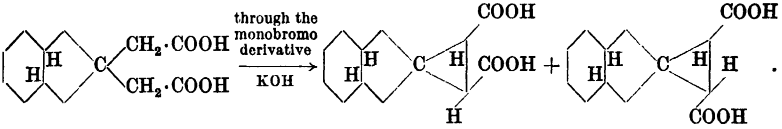


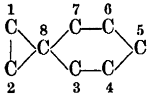
Potassium hydroxide decomposes the compound back to cyclopropane dicarboxylic acid and succinic acid (*Radulescu*, Ber. **42**, 2770; **44**, 1018).

Cyclopentane-spiro-methylcyclopropane-1,2-ω,ω-tetracarboxylic acid, *Et_4-ester* $C_{20}H_{30}O_8$, b.p. 245–253°/11 mm., is obtained from cyclopentane-1,1-α,α-dibromo-diacetic ester with sodiomalonic ester (*Ingold, Lanfear, Thorpe,* J. **123**, 3147):



1,2-Dicarboxy-cyclopropane-3,2′-spiro-trans-hexahydrohydrindene, $C_{13}H_{18}O_4$, cis m.p. 225°, trans m.p. 262°, can be synthesised by the following general method (*Kandiah*, J. **1931**, 952):



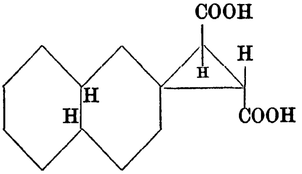


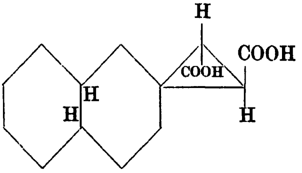
THE SPIRO-[2,5]-OCTANE SYSTEM

Cyclohexane-spiro-cyclopropane-1,2-dicarboxylic acid $C_{10}H_{14}O_4$ see *Basley*, J. **107**, 1080.

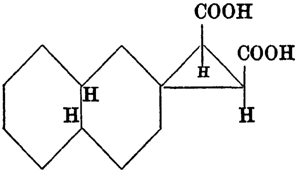
5-Methyl-cyclohexane-spiro-cyclopropane-1,2-dicarboxylic acid $C_{11}H_{16}O_4$, cis form m.p. 165°, trans form m.p. 212°, can be made by the cyanacetic ester method (*Desai*, J. **1932**, 1047). The stability of cyclohexane-spiro-cyclopropane is much reduced by the introduction of the methyl substituent, so that the dicyano-imide is easily decomposed by KOH to α,β-dicyano-1-hydroxy-3-methyl-cyclohexyl-succinic acid m.p. 212° (*Birch, Thorpe,* J. **121**, 1821).

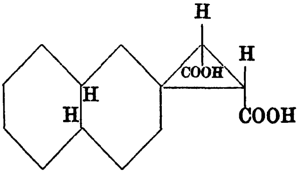
Of trans **decalin-β,1-spiro-cyclopropane-2,3-dicarboxylic acid** $C_{14}H_{20}O_4$ four isomeric forms are theoretically possible; three of them have been isolated (*Rao*, J. **1930**, 1162):



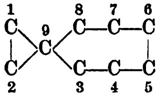


m.p. 264° trans-Forms m.p. 250°



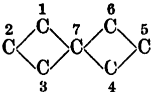


m.p. 186° cis-Forms not isolated



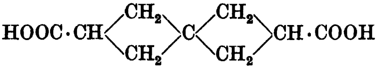
THE SPIRO-[2,6]-NONANE SYSTEM

Cycloheptane-spiro-cyclopropane-1,2-dicarboxylic acid $C_{11}H_{16}O_4$, trans form, m.p. 235°, is prepared by condensation of cycloheptanone with two molecules of cyanacetic ester to cycloheptane-diacetic acid and ring closure of its monobromo ester (*Baker, Ingold,* J. **123**, 122).

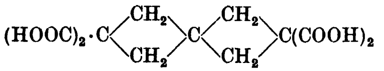


THE SPIRO-[3,3]-HEPTANE SYSTEM

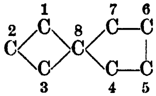
Spiro-dicyclobutane-2,5-dicarboxylic acid, m.p. 212°,



and **Spiro-dicyclobutane-2,2,5,5-tetracarboxylic acid,** m.p. 219°,



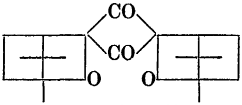
can be obtained from penterythritol tetrabromohydrin (I, 650) and malonic ester with amyl-alcoholic sodium hydroxide (*Fecht,* Ber. **40**, 3383). The tetracarboxylic acid loses CO_2 on melting and gives the dicarboxylic acid. The latter has been resolved by means of its brucine salt, $[\alpha_D]$ + 1·9° (*Becker,* Rec. **50**, 921).



THE SPIRO-[3,4]-OCTANE SYSTEM

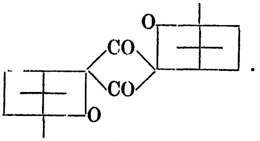
Cyclopentane-spiro-cyclobutane-1,1,3,3-tetracarboxylic acid $C_{12}H_{14}O_8$, m.p. 190°, has been prepared from cyclopentanone and cyanacetic ester. The dicyano-imide first formed is converted into its sodium compound, treated with methylene iodide and finally hydrolysed (*Paul,* J. Ind. Ch. Soc. **8** (1931), 717).

Dicampho-cyclobutadione is known in two stereo-isomeric forms and can be prepared from camphor-carboxylic chloride and quinoline (*Staudinger,* Ber. **53**, 1110):

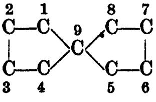


m.p. 152–153°

and



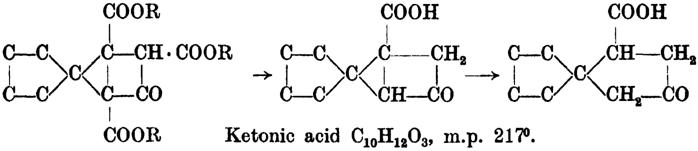
m.p. 150–151°.



THE SPIRO-[4,4]-NONANE SYSTEM

2-Methyl-cyclopentane-spiro-cyclopentane-5,7-dione, $C_{10}H_{14}O_2$, m.p. 101°, is formed by condensation of 1-acetyl-3-methyl-cyclopentane-1-acetic ester by means of NaOEt (*Dickens, Kon, Thorpe,* J. **121**, 1496).

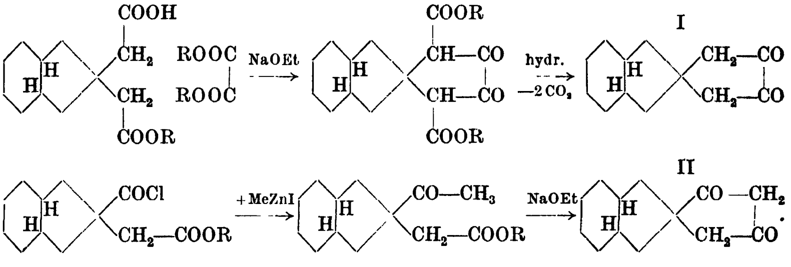
Cyclopentane-spiro-cyclopentane-3-one-1-carboxylic acid, $C_{10}H_{14}O_3$, m.p. 74°, is obtained from the condensation product of ethyl cyclopentane-spiro-methyl-cyclopropane-tetracarboxylate (p. 157) by hydrolysis, decarboxylation and reduction with sodium amalgam (*Ingold, Lanfear, Thorpe,* J. **123,** 3147):



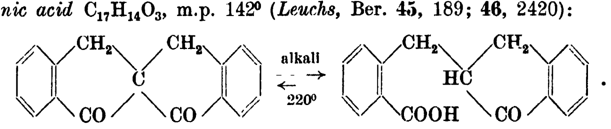
Ketonic acid $C_{10}H_{12}O_3$, m.p. 217°.

2-Methyl-cyclopentane-spiro-6,7-diketo-cyclopentane-5,8-dicarboxylic acid, *dimethyl ester* $C_{14}H_{18}O_6$, m.p. 125°, is the condensation product of 3-methyl-cyclopentane-1,1-diacetic ester and dimethyl oxalate (*Desai,* J. **1932,** 1047).

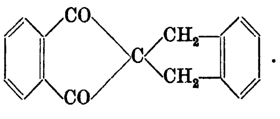
Cyclopentane-3,4-dione-1,β-spiro-trans-hexahydro-hydrindene (I) $C_{13}H_{18}O_2$, m.p.111°, and its isomer, the corresponding **2,4-dione** (II) m.p. 190°, were prepared by the following methods (*Kandiah,* J. **1931,** 952):



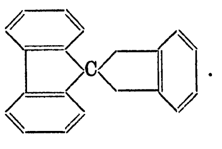
Bis-hydrindone-spirane $C_{17}H_{12}O_2$, m.p. 174° (*oxime* m.p. 215°), from dibenzyl-malonic chloride with $AlCl_3$ (cf. general methods of synthesis p. 155), is a 1,3-diketone, and hence undergoes reversible decomposition into a *ketonic acid* $C_{17}H_{14}O_3$, m.p. 142° (*Leuchs,* Ber. **45,** 189; **46,** 2420):

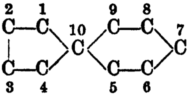


The isomeric **xylylene-diketo-hydrindene,** m.p. 150°, is a yellow compound prepared from diketo-hydrindene and o-xylylene dibromide (*Fecht,* Ber. **40,** 3883):



Xylylene-fluorene $C_{21}H_{16}$, m.p. 220°, is a condensation product of fluorene and o-xylylene dibromide (id. ib.):



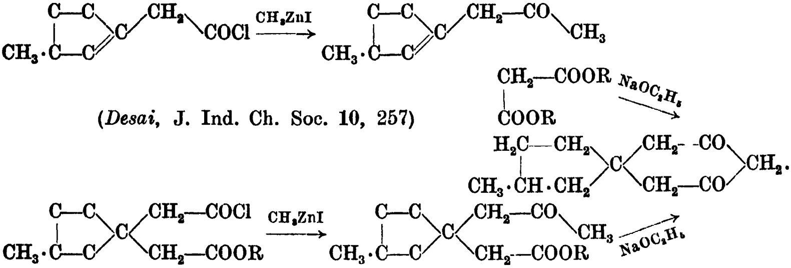


THE SPIRO-[4,5]-DECANE SYSTEM

Cyclopentane-spiro-cyclohexane, m.p. 185–186°, is obtained from the hydrazone of cyclopentane-spiro-cyclohexanone-5 by treatment with KOH (*Zelinsky*, Ber. **62**, 2180).

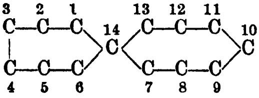
Cyclopentane-spiro-cyclohexanone-5, $C_{10}H_{16}O$, b.p. 225–227° (*oxime* m.p. 55–60°), is prepared from dicyclopentyl-1,1′-diol (*Meiser*, Ber. **32**, 2055), or from 9,10-octalin-diol by the action of H_2SO_4 (*Hückel*, Ann. **474**, 121; *Clemo*, J. **1932**, 1778). Its formula has been given in the section dealing with general methods of preparation (p. 155). Its constitution has been established by oxidation with HNO_3 to *cyclopentane-1-carboxylic-1-butyric acid* $C_{10}H_{16}O_4$ (*Meiser*, l. c.).

2-Methyl-cyclopentane-spiro-cyclohexandione-6,8, $C_{11}H_{16}O_2$, m.p. 128°, has been synthesised by two methods, both starting from 5-ring derivatives:



(*Desai*, J. Ind. Ch. Soc. **10**, 257)

Cyclohexane-3,5-dione-1,β-spiro-trans-hexahydrohydrindene, $C_{14}H_{20}O_2$, m.p. 199°, can be prepared by the action of MeZnI on trans hexahydrohydrindene-diacetic-ester-chloride and subsequent condensation by means of NaOEt (*Kandiah*, J. **1931**, 952).



THE SPIRO-[6,7]-TETRADECANE SYSTEM

Cycloheptane-spiro-cyclo-octanone-7, $C_{14}H_{24}O$, m.p. 72°, is formed by ring enlargement from 1,1′-dihydroxy-dicycloheptyl (p. 153) on boiling with dilute H_2SO_4 or with aqueous oxalic acid (*Godchot*, C. r. **186**, 767).

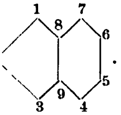
3. CONDENSED CYCLIC SYSTEMS

Condensed saturated ring systems occur in a certain number of natural products, such as the bicyclic terpenes and the sterol derivatives, etc., which are discussed in later sections. This section deals mainly with the compounds containing condensed rings which have been prepared by synthetical methods. Such methods are similar in principle to those used for preparing simple monocyclic compounds, and the more important are;

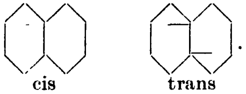
Application of the *Wurtz* synthesis to cyclic dibromides.
Elimination of hydrogen halide from cyclic monohalides.
Condensation of cyclic dicarboxylic esters by *Dieckmann's* method.

Formation of ketones from cyclic dicarboxylic acids.
Condensation of cyclic olefins by means of acids.
Interaction of diazo compounds and cyclic unsaturated compounds.
Application of the diene synthesis of *Diels* and *Alder*.

The nomenclature used can be explained by the example of decalin, which according to *Baeyer's* rules is called bicyclo-[0,4,4]-decane, the first figure 0 denoting the number of bridging carbons, and the two following figures 4,4 showing the number of ring members united to the bridge. Where unequal rings are condensed together, as in cyclopentano-cyclohexane, the numbering begins with the smaller ring and ends with the two carbons which are common to both rings:



The stereochemistry of this group is especially interesting (see *Linstead*, Ann. Rep. Chem. Soc. 1935, **32**, 305; *Mills*, Dict. of Applied Chemistry, Supplement **1935**, Vol. II, 433; *W. Huckel*, Der gegenwärtige Stand der Spannungstheorie, 1928). To take the decalin system of two condensed six-membered rings as an example, it is known that each separate ring can exist in a multiplanar strainless configuration, and hence there is the possibility that two such rings can be united in two ways, in one of which cis valencies are involved and in the other trans valencies. The actual existence of such isomers was first established by *W. Huckel*, who obtained the isomeric decalins. The formulae of these compounds can be written as:



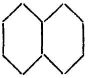
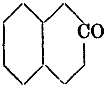
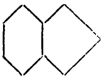
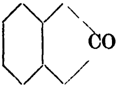
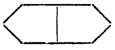
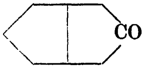
Here the plain hexagons imply cyclohexane, and not benzene, rings, and the valencies at the ring junction are carrying hydrogen atoms and show whether cis or trans valencies are involved in the linking between the rings. There is the same possibility whenever two saturated rings are condensed, but the strain which is set up as a result of the two methods of linking is different according to the number of atoms in the rings; with the smaller rings there must clearly be a deformation of each single ring from its least strained configuration for trans linking to take place, while with the larger rings no such deformation is needed. By simple calculation and the use of models (see *Mills*, loc. cit.), the strain involved in the various combinations of rings can be estimated on the assumption that the greater the departures from the tetrahedral angles the greater the strain. The results so predicted for five and six membered rings are as follows.

(1) Two five-membered rings can be fused by cis valencies to give a strain-free rigid structure of two inclined planar rings, while fusion by trans valencies should give a strained multiplanar structure in which the strain is about the same as in the bicyclo-[1,2,2]-heptane system that occurs in camphor.

(II) Two six-membered rings can be joined either by cis or trans valencies to give strainless multiplanar systems.

(III) A five-ring can be joined to a six-ring by cis valencies to give a strainless system in which the five-ring is flat and the six-ring is of the boat shape. With trans valencies a strained multiplanar structure results in which the strain is about half that in the trans linking of two five-rings.

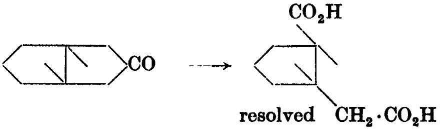
These predictions, on the whole, are verified by the actual measurements of the energy content of the isomeric compounds which have been obtained. The most accurate method so far used for measuring this is by the heats of combustion, a higher heat corresponding to a greater energy content and hence a more strained system. The following table of typical results gives the heat of combustion in k.cal. per mole of liquid at constant volume.

Substance		Cis form	Trans from	Diff. trans-cis	Ref.
Decalin		1499·9	1495·2	—4·7	a
β-Decalone		1402·3	1400·1	—2·2	a
Hydrindane		1347·5	1345·7	—1·8	b
β-Hydrindanone		1245	1243·9	—1·1	b, c
Bicyclo-[0, 3, 3] octane		1197·7	1203·8	+ 6·1	d
β-Bicyclo-octanone		1094·1	1100·9	+ 6·9	e

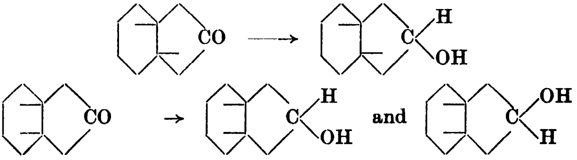
(a) *Roth*, Ann. **441**, 48; (b) *W. Hückel* et al., Ann. **518**, 155; (c) *W. Hückel, Friedrich*, Ann. **451**, 132; (d) *Barrett, Linstead*, J. **1936**, 611; (e) *Idem*, J. **1935**, 436.

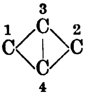
The divergences from the predictions are that the cis hydrindane system is slightly more strained than the trans, the opposite to the effect expected, and that in the decalin system the trans form has less energy than the cis, though both forms should be strainless. These facts must be due to other effects which come into play and are not included in the simple strain theory.

The configurations of the isomers in the three ring systems shown in the table above have been established quite rigorously. For the decalin and bicyclo-octane series this has been done by oxidising the β-ketones to carboxy-acetic acids of cyclohexane and cyclopentane respectively; the two isomeric ketones give isomeric acids, and in each series one of these acids has been resolved into its optical antimers. These active acids must be trans acids, and hence the configurations of the ketones follow (*W. Hückel* et al., Ann. **518**, 155; *Barrett, Linstead,* J. **1935**, 1069).



In the hydrindane series the evidence comes from the reduction of the β-hydrindanones; the trans ketone should give one racemic trans hydrindanol, while the cis ketone should give two isomeric meso cis hydrindanols. These isomers have been isolated (*W. Hückel, Friedrich,* Ann. **451**, 132).

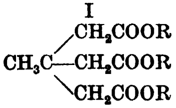




THE BICYCLO-[0,1,1]-BUTANE SYSTEM

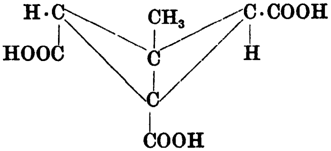
1-Methyl-bicyclo-[0,1,1]-butane-2,3,4-tricarboxylic acids (3-methyl-cyclopropano-cyclopropane-1,2,4-tricarboxylic acids). Condensed systems of two cyclopropane rings have been obtained starting from ethenyl-triacetic ester $CH_3 \cdot C(CH_2COOC_2H_5)_3$ (I) by the bromination of two H-atoms in the α-position and eliminating two HBr. Three stereo-isomers are formed (II, III, IV):

I



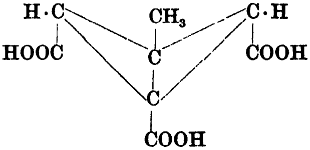
$$CH_3C(CH_2COOR)_3$$

II



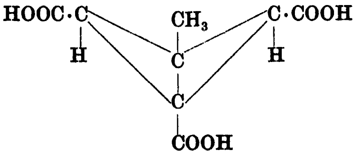
rac. form, m.p. 66°

III



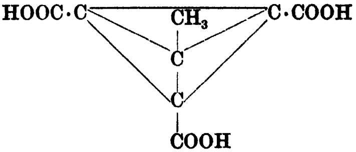
meso-cis-form, m.p. 154°

IV



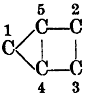
meso-trans-form m.p. 193°

V



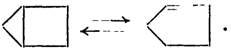
m.p. 149°.

Bromination of the meso-cis or of the meso-trans acid and elimination of HBr results in the **tetracyclic acid** (V) m.p. 149°. For the nomenclature of these ring systems see *Beesley, Thorpe, Ingold,* J. **117**, 591.



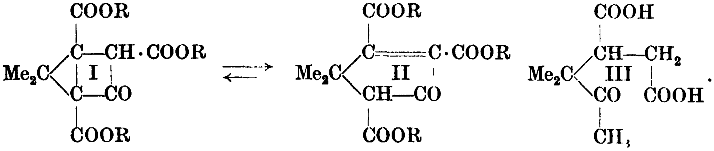
THE BICYCLO-[0,1,2]-PENTANE SYSTEM

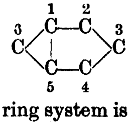
The ring combination of cyclopropane and cyclobutane seems sometimes to be able to react in a tautomeric monocyclic form



While the three-membered ring formula is suggested by the formation of caronic acid as an oxidation product of certain derivatives of this system (*Farmer, Ingold,* J. **117**, 1362), the optical evidence and many of the chemical properties indicate the cyclopentene structure (*Toivonen,* C. 1927 II 1248). Important decomposition reactions of this ring system have been mentioned in the sections on cyclopentene derivatives (p. 49) and on spiranes (p. 159). The ring system is obtained both by condensing substituted dibromoglutaric acids with malonic ester and also by condensing cyclopropane-dicarboxylic acids with cyanacetic ester (*Goss,* J. **1928**, 1268).

1,1-Dimethyl-cyclopropano-cyclobutane-3-one-2,4,5-tricarboxylic ester (I) or *1,1-dimethyl-Δ^2-cyclopentene-4-one-2,3,5-tricarboxylic ester* (II) (*Perkin,* Ber. **35**, 2126; *Radulescu,* Ber. **42**, 2770) is formed by condensation of α, α_1-dibromo-β-dimethyl-glutaric ester with Na-malonic ester, a dimethyl-cyclopropane dicarboxylic-malonic ester being an intermediate product. The methylation product obtained by treatment with MeI, 1,1,5-trimethyl-Δ^2-cyclopentene-4-one-2,3,5-tricarboxylic ester, must be a derivative of II, because the compound obtained by hydrogenation is converted by decarboxylation and oxidation with $KMnO_4$ into the ketonic acid (III); by further degradation by means of HOCl the latter gives α, α-dimethyltricarballylic acid. Furthermore, reduction of the hydrogenation product yields first 5-keto-camphoric acid and then camphoric acid (p. 304) (*Toivonen,* ibid.):



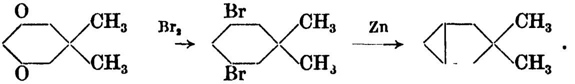


THE BICYCLO-[0,1,3]-HEXANE SYSTEM

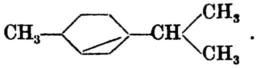
This ring system is found in a few natural terpenic compounds. It has been synthesised from cyclopropane derivatives, from cyclopentane derivatives and also from hydroaromatic compounds. The bridge linkage is easily broken both by hydration and by dehydration, hydroaromatic compounds being formed in the one case, and aromatic in the other. Oxidation and reduction give cyclopentane derivatives by opening of the 3-ring and cyclopropane derivatives by breaking of the 5-ring (cf. Terpenes).

Bicyclo-[0,1,3]-hexane, cyclopropano-cyclopentane, b.p. 80–81°, is formed from 1-bromo-cyclopentyl-2-methyl bromide by action of Zn and alcohol (*Zelinsky,* Bull. **35** (1924), 484), and also from cyclopentylmethyl iodide by elimination of hydrogen iodide (*Zelinsky,* Ber. **66**, 1422).

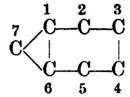
Another example of the condensed three- and five-ring system is **3,3-dimethyl-bicyclo-[0,1,3]-hexane, cyclopropano-3,3-dimethyl-cyclopentane** b.p. 115°, which can be synthesised from dimethyl-dihydroresorcinol (p. 112) via the corresponding dibromide (id., Ber. **46**, 1466).



4-Methyl-1-isopropyl-bicyclo-[0,1,3]-hexane, *sabinane, thujane,* is of importance as the parent hydrocarbon of sabinene, α-thujene, the terpene alcohols sabinol, thujyl alcohol and the ketones thujone and umbellulone (cf. Terpenes). Its constitution is



The ring system can be built up synthetically by *Dieckmann's* method, for example, thujone from α-thujaketonic acid (*Ruzicka,* Helv. **15**, 944; see p. 243). The system can rearrange into an unsaturated 6-ring (carvotanacetone) or into an unsaturated 5-ring (isothujone) cf. p. 244. Copaene (p. 332) and ledum-camphor (p. 336) are derived from the bicyclo-[0,1,3]-hexane skeleton united to another 6-ring.

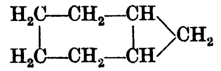


THE BICYCLO-[0,1,4]-HEPTANE SYSTEM

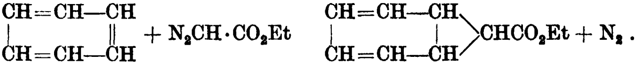
3-Methyl-bicyclo-[0,1,4]-heptane ("*octanaphthylene*"), *cyclopropano-1-methyl-cyclohexane,* C_8H_{14}, b.p. 118–121°, smells like a terpene. It is obtained from the "octanaphthene" occurring in Bibi-Eibat naphtha by preparing chloro-octa-naphthene, heating this with CaI_2 and treating the resulting iodide with moist silver oxide (*Markovnikov,* Ber. **18**, R. 186; **30**, 1219) or with zinc dust in benzene (*Joukovsky,* Bull. **16** (1896), 127).

This ring system is found in the carane group (p. 246), which comprises the carenes, naturally occurring hydrocarbons, and the compounds carone and carane which are synthetical products.

The parent substance of this group is the hydrocarbon:



which because of its relation to carene is called **norcarane.** The ring system can be synthesised by a general method, which consists in heating diazo-acetic ester (I 458) with benzene or its derivatives (*Buchner,* Ber. **33**, 3453; **34**, 982; **36**, 3502; **37**, 931; see p. 21)



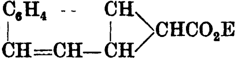
$\Delta^{2,4}$-Norcaradiene-7-carboxylic ethyl ester, *$\Delta^{4,6}$-bicyclo-[0,1,4]-heptadiene-7-carboxylic ethyl ester, cyclopropano-$\Delta^{2,4}$-cyclohexadiene-7-carboxylic ethyl ester, ψ-phenylacetic ester,* $C_6H_6 > CHCO_2Et$ is obtained by heating benzene and diazo-acetic ester under pressure to 135–140°. The ester, b.p. 108°/13 mm., gives a cherry-red colour with conc. H_2SO_4 which changes to indigo blue, and is partially converted into β-cycloheptatriene carboxylic ester; with ammonia it forms a crystalline *amide,* m.p. 141°, which is hydrolysed by sulphuric acid to the *free acid,* an oil at room temperature. The acid gives with bromine a *dibromide,* m.p. 160° decomp., and a *tetrabromide,* m.p. 235° decomp. Its oxidation with permanganate is complicated: benzoic acid, o- and p-phthalic acids and, by breaking the 6-ring, cyclopropane tricarboxylic acid are formed. Heating the ester under pressure transforms it into β-cycloheptatriene carboxylic ester (p. 73), and boiling the ester or the amide with alkali gives α-cycloheptatriene carboxylic acid (the cyclopropane ring splitting between 1 and 6). Conc. sulphuric acid converts the amide into phenyl-acetamide $C_6H_5CH_2CONH_2$ (the cyclopropane ring splitting between 1 and 7). Cf. the analogous reactions of carone p. 248.

$\Delta^{2,4}$-3-Methyl-norcaradiene carboxylic ester, *ψ-tolylacetic ester* $CH_3 \cdot C_6H_5 > CHCO_2Et$, b.p. 122–126°/12 mm., from toluene and diazoacetic ester, *amide* m.p. 131°, yields p-tolylacetic acid when boiled with 30% sulphuric acid, and is converted into methyl-cycloheptatriene carboxylic acid, m.p. 108°, by prolonged shaking with ammonia followed by hydrolysis with 30% H_2SO_4.

3,5-Dimethyl-norcaradiene carboxylic ester, *ψ-xylylacetic ester* $(CH_3)_2C_6H_4 > CHCO_2Et$, b.p. 125–135°/10 mm., from m-xylene and diazo-acetic ester; *amide*, m.p. 142°, yields 2,4-xylylacetic acid with H_2SO_4 (*Buchner*, Ann. **358**, 1).

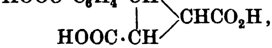
1,7-Norcarane dicarboxylic ester $C_2H_5OCO \cdot C_6H_9 > CH \cdot COOEt$, b.p. 160°/18 mm. from Δ^1-tetrahydrobenzoic ester (p. 131) with diazo-acetic ester. The acid, m.p. 153°, yields an *anhydride* m.p. 87°.

Benznorcaradiene carboxylic ester



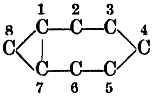
$$\begin{array}{l} C_6H_4 - - CH \\ | \qquad\qquad\quad | \; > CHCO_2Et \\ CH{=}CH{-}CH \end{array}$$

b.p. 163–164°/11 mm., from naphthalene (vol. III) with diazo-acetic ester, gives an *acid* m.p. 166°, *amide* m.p. 217°. Oxidation produces *carboxy-phenyl-cyclopropane dicarboxylic acid*



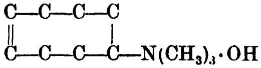
$$\begin{array}{l} HOOC \cdot C_6H_4 \cdot CH \\ \qquad\qquad\quad | \; > CHCO_2H \\ \quad HOOC \cdot CH \end{array}$$

which is further degraded to cyclopropane-1,2,3-tricarboxylic acid (p. 33).



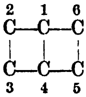
THE BICYCLO-[0,1,5]-OCTANE SYSTEM

Bicyclo-[0,1,5]-octene, *cyclopropano-cycloheptene*, C_8H_{12}, b.p. 137–139°, has a high refractive index, and an odour resembling that of tropilidene. It is formed, together with cyclo-octadiene-1,5, by distilling granatanin-trimethyl-ammonium hydroxide:



The bromides are fractionated and the hydrocarbon is regenerated with quinoline (*Willstätter*, Ber. **40**, 957; *Harries*, Ber. **41**, 672). Permanganate oxidises it to a hydroxyketone $C_8H_{12}O_2$ (*semicarbazone* decomp. 251°), ozone gives a *mono-ozonide* $C_8H_{12}O_3$. Catalytic hydrogenation by the method of *Sabatier* and *Senderens* gives the saturated:

Bicyclo-[0,1,5]-octane, *cyclopropano-cycloheptane* C_8H_{14}, b.p. 139·5–140·5°, the bicyclic character of which is confirmed by its molecular refraction (*Willstatter*, Ber. **41**, 1485).

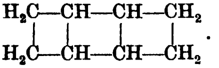


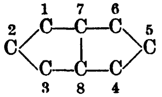
THE BICYCLO-[0,2,2]-HEXANE SYSTEM

An attempt to prepare the parent hydrocarbon of this ring system, **bicyclo-[0,2,2]-hexane** (cyclobutano-cyclobutane) by treating cis 1,4-dibromo-cyclohexane with metallic sodium in abs. amyl ether (*Zelinsky*, Ber. **60**, 1102) resulted in a mixture of $\Delta^{1,3}$-cyclohexadiene, cyclohexene and cyclohexane. The value of the parachor of the product shows that a bicyclic system is not formed (*Prjashnikov*, Ber. **67**, 64). $\Delta^{1,3}$-Cyclohexadiene is also formed from trans 1,4-dibromo-cyclohexane under the same conditions.

Tricyclo-octane, dimethyl-tricyclo-octane and diphenyl-tricyclo-octane. The di-alkylene carboxylic acids, vinyl-acrylic acid, sorbic acid and styryl-acrylic acid, polymerise when heated with $Ba(OH)_2$, with loss of CO_2. The hydrocarbons so obtained are regarded as tricyclo-octanes, though the evidence is not entirely satisfactory (*Doebner*, Ber. **40**, 146).

Tricyclo-octane, C_8H_{12}, b.p. 50–52°/27 mm. (*Perkin*, Ber. **35**,21 34; *Willstätter*, Ber. **38**, 1976):





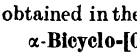
THE BICYCLO-[0,3,3]-OCTANE SYSTEM

(Pentalane System)

In this group the cis compounds are more stable than the trans, as has been mentioned above, and this is a valuable confirmation of the strain theory for such systems. No compounds containing this ring system are known to occur in nature, but they can be synthesized by the ordinary methods.

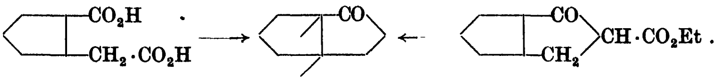
A series of compounds obtained by *Willstätter* from the alkaloid ψ-pelletierine (Ber. **41**, 1485) was formerly allotted to this group, and a saturated hydrocarbon he prepared, which is identical with one synthesized by *Schroeter* (Ann. **426**, 1), was held to be the parent substance of the class. The synthesis, however, affords no proof of the structure and it is probable that the bridge is in another position.

Bicyclo-[0,3,3]-octane, *cyclopentano-cyclopentane*; the cis form, b.p. 136°/755 mm., n_D^{18} 1·4629, d_4^{18} 0·8718, is obtained by the reduction of cis-β-bicyclo-octanone or of the corresponding α-ketone, either by Clemmensen's method or by that of Wolff (*Linstead*, J. **1934**, 945, 956). When heated with $AlCl_3$ (id., J. **1936**, 611), it rearranges into bicyclo-[1,2,3]-octane,



, which has been synthesized by *Komppa* (Ann. **521**, 242). The trans form, b.p. 132°/755 mm., m.p. —30°, n_D^{18} 1·4625, d_4^{18} 0·8626, is obtained in the same way from trans β-bicyclo-octanone (*Linstead*, J. **1935**, 442).

α-Bicyclo-[0,3,3]-octanone, 72°/12 mm., *semicarbazone* m.p. 181°, only exists in the cis form because the position of the CO group adjacent to the bridge head facilitates the rearrangement of the strained trans form into the more stable cis form. The ketone is obtained when either cis or trans 2-carboxylcyclopentane-propionic acid is heated with a trace of baryta, and also by the Dieckmann condensation of the diethyl esters of these acids, followed by hydrolysis of the ketonic ester (*Linstead*, J. **1934**, 946).

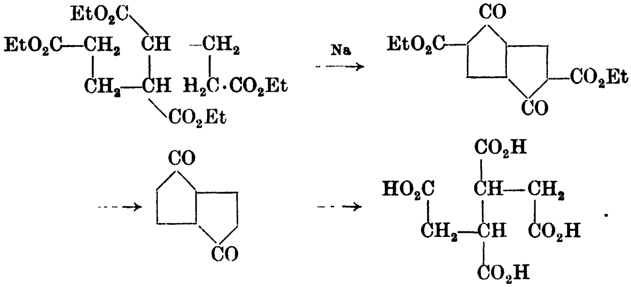


The β-ketone is known in both cis and trans forms, the configurations of which have been established by oxidation to the 2-carboxy-cyclopentane-acetic acids whose configurations are known.

β-Bicyclo-[0,3,3]-octanone; the cis form, 195°/755 mm., 78°/10 mm., m.p. —28°, *semicarbazone* m.p. 198°, is obtained by distilling cis cyclopentane-

1,2-diacetic acid with baryta at 280°, and also by hydrolysis of the *ketonic ester*, b.p. 136°/17 mm., obtained by treating the ester of the same acid with molecular sodium (*Linstead*, J. **1934**, 944). The ketone is oxidised by HNO_3 to cis 2-carboxy-cyclopentane-acetic acid (p. 67). The trans form, b.p. 189°/755 mm., 62°/10 mm., m.p. 18°, *semicarbazone* m.p. 251°, is obtained by heating trans cyclopentane-1,2-diacetic acid with baryta to 340°. Dieckmann condensation of the ester of this acid does not take place because of ring strain. The ketone is oxidised to trans 2-carboxy-cyclopentane-acetic acid (p. 67). The trans diacetic acid can be resolved, its configuration being thus established, and if the *l*,acid is heated, the dextrorotatory ketone is formed, m.p. 41°, $[\alpha]^{18}$ 437°. This gives an inactive bicyclo-octane when reduced (*Linstead*, J. **1935**, 1069).

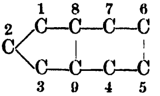
Bicyclo-[0,3,3]-octane-1,4-dione, m.p. 45°, *dibenzylidene compound* m.p. 240°, has been synthesized by the Dieckmann condensation (Na in benzene) of hexane-1,3,4,6-tetracarboxylic ester; double ring closure takes place. The product, *bicyclo-octane-1,4-dione-2,5-dicarboxylic ester* m.p. 57·5°, is hydrolysed with loss of CO_2.



With amyl formate a 2,5-dihydroxy-methylene compound is formed, which is oxidised by ozone to butane-1,2,3,4-tetracarboxylic acid (*Ruzicka*, Helv. **17**, 183).

Attempts to dehydrogenate the bicyclo-[0,3,3]-octane system to an unsaturated ring, using selenium, were unsuccessful, and the ring system is also stable to hydrogenation (*Linstead*, J. **1936**, 611). The product obtained by the continued action of $AlCl_3$ on decalin is probably 1,4-dimethyl-bicyclo-[0,3,3]-octane (*Id. ibid.* 616).

A mixture of stereoisomeric forms of *bicyclo-[0,3,3]-octane-1-one-3-carboxylic acid* has been obtained by *Bardhan* and *Banerji* (J. **1935**, 474).

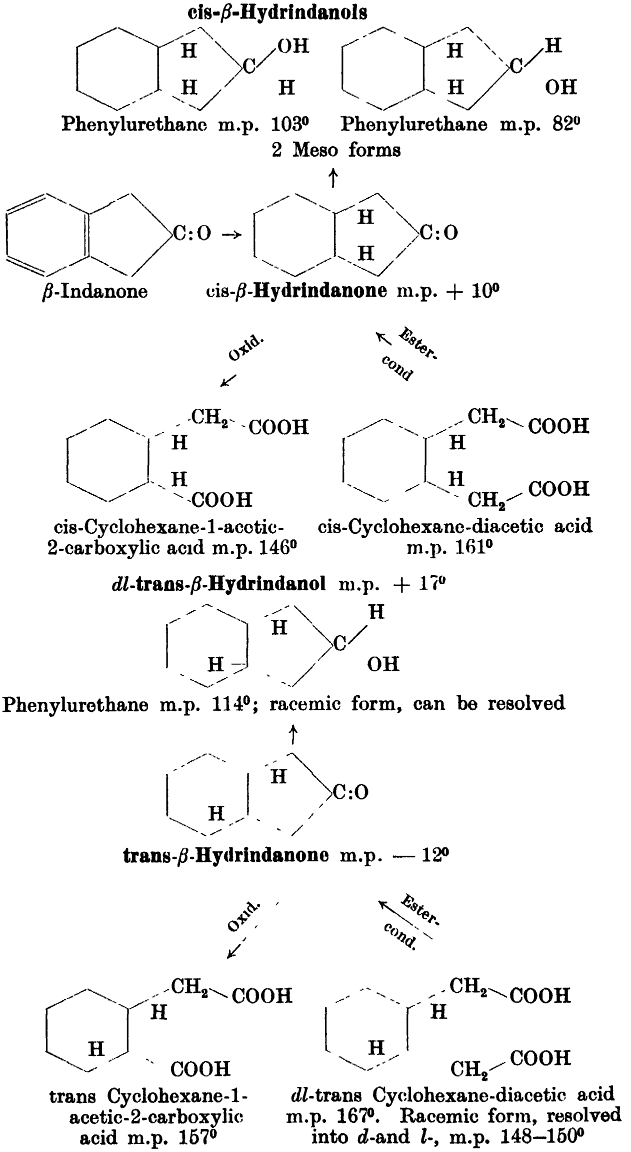


THE BICYCLO-[0,3,4]-NONANE SYSTEM

(Hydrindane System)

Bicyclo-[0,3,4]-nonane (*hydrindane*), *cyclopentano-cyclohexane*, C_9H_{16}, b.p. 163–164°, obtained by catalytic hydrogenation of hydrindene with Ni (*Eijkman*, Chem. Weekbl. **1**, 7; **3**, 653; **4**, 41). It can also be obtained from carboxy-cyclohexane-propionic acid and cyclohexane-diacetic acid by ring synthesis, α- and β-hydrindanone being intermediates.

The 5-ring can be linked to the 6-ring both by cis and trans valencies. The stereo-chemistry of this ring combination is illustrated by the following diagrams, which represent the relations of the three possible isomeric β-hydrindanols to cis and trans β-hydrindanone. The evidence for the configuration shown comes from the methods of formation, the degradation to carboxylic acids of the cyclohexane series of known configuration, and the resolution of the trans compounds into optical antimers (*Hückel*, Ann. **451**, 132; *Linstead*, J. **1935**, 1069):



cis-β-Hydrindanols

Phenylurethane m.p. 103° Phenylurethane m.p. 82°

2 Meso forms

β-Indanone cis-β-**Hydrindanone** m.p. + 10°

cis-Cyclohexane-1-acetic-2-carboxylic acid m.p. 146°

cis-Cyclohexane-diacetic acid m.p. 161°

dl-**trans-β-Hydrindanol** m.p. + 17°

Phenylurethane m.p. 114°; racemic form, can be resolved

trans-β-Hydrindanone m.p. — 12°

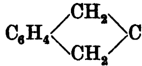
trans Cyclohexane-1-acetic-2-carboxylic acid m.p. 157°

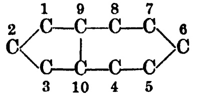
dl-trans Cyclohexane-diacetic acid m.p. 167°. Racemic form, resolved into *d*-and *l*-, m.p. 148–150°

Cis and trans cyclohexane-1-acetic-2-carboxylic acids are prepared by reducing homophthalic acid. Cis and trans cyclohexane-diacetic acids are obtained from cis-β-decalol, m.p. 105°, and trans-β-decalol, m.p. 75°, resp. and by the hydrogenation of o-phenylene-diacetic acid.

In the α-series, where the CO group is next to one of the carbon atoms common to both rings, interconversion of the cis and trans isomers takes place much more readily, the intermediate being presumably the enolic form. Ring closure of both the cis and trans forms of 2-carboxy-cyclohexane-propionic acid, and also the Dieckmann condensation of their esters, gives the same mixture of the two stereoisomers, in which the cis form greatly predominates (*W. Hückel et al.*, Ann. **518**, 155). A number of hydrindanones substituted in the six-ring are also known (*W. Hückel*, Ber. **67**, 2104, 2107; *Linstead*, J. **1934**, 946).

Hydrindane-2,2-diacetic acid, $C_{13}H_{20}O_4$, occurs, like its parent substance β-hydrindanone, in two stereo-isomeric forms. The cis form melts at 188° and yields two *anilic acids* m.p. 184° and 180°; *anil* m.p. 140°. The trans form melts at 224°, its *anilic acid* at 203°, its *anil* at 197° (*Kandiah*, J. **1931**, 952). The synthesis starts from β-hydrindanone, which is condensed with cyanacetic ester to the *dicyano-imide*, cis form m.p. 262°, trans form m.p. 291°.

Hydrindene 
$C_6H_4{<}\begin{matrix}CH_2\\CH_2\end{matrix}{>}CH_2$, which contains an unchanged benzene ring, and its derivatives are described in the section on indene, vol. III.

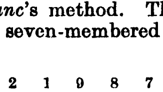


THE BICYCLO-[0,3,5]-DECANE SYSTEM

Cyclopenteno-cycloheptanone, *bicyclo-[0,3,5]-$\Delta^{9,10}$-decenone-4* $C_{10}H_{14}O$, m.p. 37°, b.p. 123°/12 mm., *oxime* m.p. 134°, is formed from cyclodecanedione $C_{10}H_{16}O_2$, m.p. 101°, by intramolecular aldol condensation and subsequent elimination of water with acid or alkali (*Huckel*, Ann. **474**, 121; Ber. **66**, 563). Cyclodecanedione itself (p. 81) is obtained from $\Delta^{9,10}$-octalin (p. 173) by the action of ozone. The molecular refraction and selective light absorption indicate conjugation of the double bond and the carbonyl group. The meso position of the double bond is proved by the formation, on hydrogenation, of the cis and trans isomeric forms of

Cyclopentano-cycloheptanone, $C_{10}H_{16}O$ (*oxime* cis m.p. 119°, trans m.p. 140°). Oxidation results in δ-keto-sebacic acid (m.p. 116°), which proves that there is no side chain attached to the carbon ring.

Cyclopentano-cycloheptene, $C_{10}H_{18}$, b.p. 63·5°/8 mm obtained from the trans *oxime*, m.p. 140°, of the foregoing compound, by way of the *amine*, b.p. 97°/10 mm, is oxidised by ozone to a dicarboxylic acid, which yields α-hydrindanone (*semicarbazone* m.p. 183°) on distillation with acetic anhydride by *Blanc*'s method. This proves that the carbonyl in the ketone belongs to the seven-membered ring (*Hückel* and *Schnitzspahn*, Ann. **505**, 274).



THE BICYCLO-[0,4,4]-DECANE SYSTEM
(Decalin System)

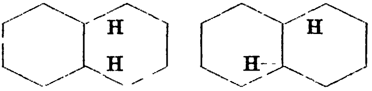
The decalin carbon skeleton is frequently met with in natural substances, e.g. sesquiterpenes and their derivatives, santonin, alantolactone, etc. Industrially, decalin derivatives are made by hydrogenation of naphthalene and its derivatives. Synthetically, those compounds are accessible by ring closure of the corresponding hydroaromatic dicarboxylic acids (*Dieckmann*) and by the diene synthesis of *Diels* and *Alder* (see quinone-butadiene-adducts, p. 175). A further general method is the condensation of acetyl-cyclohexenes with malonic ester (*Ruzicka*, Helv. **14**, 1151).

The cis and trans isomers which are derived from this ring-system are clearly distinguished by their main physical constants. The rule of *Auwers* and *Skita* is confirmed (cf. decalols and decalones);

	boiling p.	density	refractive index	molecular refraction	viscosity
cis series	higher	0·89	1·48	neg. exaltation	higher
trans series	lower	0·86	1·46	pos. exaltation	lower

By the aid of this rule it is sometimes possible to ascertain the stereochemical configurations of natural substances belonging to this system after they have been reduced to the parent hydrocarbons. Thus certain members of the sesquiterpene series: eudesmol (= 3-ethyl-5,9-dimethyl-decalin), selinene (= 3-ethyl-9-methyl-decalin) and cadinene have been found to belong to the cis series (*Ruzicka*, Helv. **14**, 1171). The rule has also been successfully applied to compounds of complicated ring structure; see sterols and bile acids (p. 557).

Decalin, *decahydro-naphthalene*, $C_{10}H_{18}$ is the parent hydrocarbon of this series. Special interest attaches to decalin and its derivatives, because they were the first group in which *W. Huckel* proved the existence of cis and trans isomers of bicyclic ring sytems (cf. p. 161) (*Huckel*, Ber. **55**, 230; Ann. **441**, 1; *Rao*, J. **1930**, 1162).



cis-Form trans-Form

Cis decalin, b.p. 193°/753 mm., m.p. — 51° (*hexabromide* m.p. 312°). *Trans decalin* b.p. 185°/753 mm, m.p. — 36° (*hexabromide* m.p. 269°), are prepared by catalytic hydrogenation of naphthalene. With a platinum catalyst cis decalin is the main product, while hydrogenation in the gas phase by *Sabatier*'s method gives mainly trans decalin. The commercial product melts at — 105°. Other methods of preparation are the reduction of the decalones (p. 172) and the hydrogenation of octalins (p. 173) (*Ipatiev*, Ber. **40**, 1287; *Willstatter*, ib. **45**, 1475; *Eisenlohr*, ib. **57**, 1639; *Zelinsky*, ib. **62**, 1658; id. Ann. **426**, 13; *Huckel*, ib. **441**, 42).

In presence of $AlBr_3$ cis decalin rearranges into trans decalin (*Zelinsky*, Ber. **62**, 1658; **65**, 1299).

In addition to the ring closure of cyclohexane-1-butyric-2-carboxylic acid and of cyclohexane-1-propionic-2-acetic acid, which gives α- or β-decalone, the ring system can be synthesised from acetyl-cyclohexene and malonic ester, via bicyclo-decane-1,3-dione. This method has been used for preparing a number of homologues of decalin (*Ruzicka*, Helv. **14**, 1151):

2-Methyl-decalin trans, b.p. 76°/12 mm. from β-decalone by CH_3MgI.

9-Methyl-decalin trans, b.p. 70–71°/12 mm., from 1-acetyl-2-methyl-Δ^1-cyclohexene and malonic ester.

4,9-Dimethyl-decalin cis, b.p. 85°/12 mm., from 1-acetyl-2,6-dimethyl-Δ^1-cyclohexene and malonic ester; obtained also from eudesmol.

3-Ethyl-9-methyl-decalin trans, b.p. 97–98°/12 mm., from methyl-cyclohexene, butyryl chloride and malonic ester; cis b.p. 102°/12 mm., made from β-selinene.

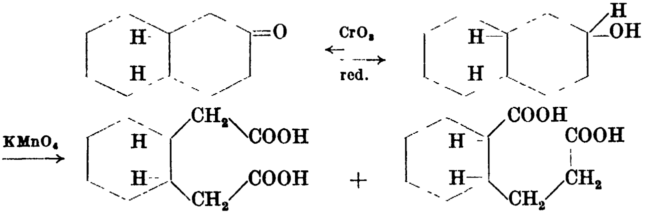
3-Ethyl-5,9-dimethyl-decalin trans, b.p. 112–113°/12 mm., from 1,3-dimethyl-cyclohexene, butyryl chloride and malonic ester; cis b.p. 116°/12 mm, obtained by rearrangement of eudesmol.

The cis-trans isomerism of the decalin system, which was predicted by *Sachse* and by *Mohr* on the ground that the cycloparaffins are multiplanar structures, has been established by the fundamentally important work of *W. Hückel* on decalols and decalones (Ann. **441**, 1; **451**, 109; **502**, 99, 114).

The following scheme shows the relationships in the cis and trans derivatives of the β-series which establish the configurations.

cis-β-Decalone $C_{10}H_{16}O$ m.p. — 14°, b.p. 128°/26 mm.

Rac. cis-β-Decalols $C_{10}H_{18}O$ m.ps. 105 and 17°

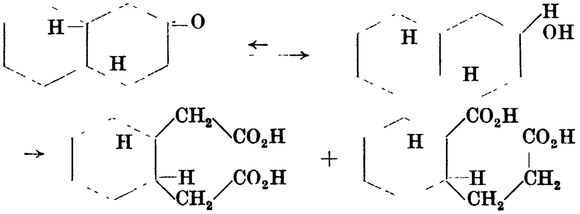


cis-Cyclohexane-1,2-diacetic acid m.p. 161°

cis-Cyclohexane-1-propionic-2-carboxylic acid m.p. 103°

trans-β-Decalone m.p. + 6°, b.p. 126°/30 mm.

rac. **trans-β-Decalols** m.ps. 75° and 53°



trans-Acid m.p. 167°, racemic form, resolved into *d* and *l*, m.p. 151°

trans-Acid m.p. 143°

cis-β-Decalols result from hydrogenation of *ac*-β-tetralol[1] with Pd by *Willstätter's* method and from cis cyclohexane-1-acetic-2-propionic acid by treatment with acetic anhydride and reduction of the decalone formed (*Hückel*, Ann. **441**, 14; Ber. **58**, 447, 1452). Similarly, trans β-decalols are obtained from *ac*-β-tetralol with a Ni catalyst. A further method for preparing both isomers is from the corresponding amines (id. Ann. **451**, 116). Theory predicts eight optically active decalols and four racemic forms. Interconversion of cis and trans isomers have been observed in the α-, though not among β-compounds (id. Ann. **441**, 21).

The decalols of the α-series, cis forms m.ps. 93° and 55°, trans forms m.ps. 63° and 49° (id. Ann. **502**, 99) are converted by the action of CrO_3 into α-decalones, cis m.p. + 2°, trans m.p. 33°, which are further oxidised by HNO_3 to cis and trans cyclohexane-1-propionic-2-carboxylic acids, m.p. 103° and 143° resp., while $KMnO_4$ converts both into the same δ-keto-sebacic acid m.p. 116°. The number of isomers is the same as in the β-series.

Decalones.—Ring closure of both cis and trans cyclohexane-1-butyric-2-carboxylic esters gives only the trans decalone of the α-series, because the cis compound rearranges readily into the trans compound, the carbonyl group being next to the point of union of the rings, where there is a H-atom. Synthesis of β-decalones has been accomplished by ring condensation of corresponding cyclohexane-1-acetic-2-propionic acids. The m.ps. are given above.

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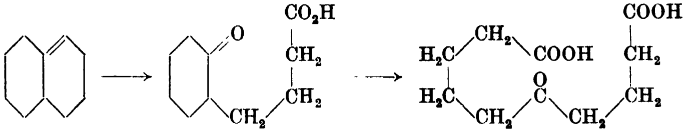
[1] See footnote p. 174.

For **Decalyl-amines** and their isomerism, see *Hückel,* Ann. **441,** 1; **451,** 109; **502,** 99. **1-Nitro-decalin,** see *Nametkin,* Ber. **59,** 370. 9-Substituted decalins see *Hückel,* Ann. **502,** 114.

Octalins (= octahydro-naphthalenes) are obtained from decalol by elimination of water and from decalyl-amine by the action of HNO_2. Six isomers are possible, which differ in the position of the double bond and in the spatial arrangement about the atoms joining the rings.

Their heats of combustion are exactly equal, but the X-ray diagrams show characteristic differences. Differences of reaction velocity have been found in hydrogenation, the action of perbenzoic acid and hydration.

$\Delta^{1,9}$-Octalin, $C_{10}H_{16}$, b.p. 189·5–193·5°, *nitrosochloride,* a colourless compound, m.p. 127°, *nitrol-piperidide,* m.p. 181°, is most conveniently prepared by the thermal decomposition of the xanthate of trans α-decalol, m.p. 63°, or by the action of HNO_2 on 9-amino-cis-decalin. Its constitution follows from the fact that on oxidation first cyclohexanone-2-butyric acid is formed, and then δ-keto-sebacic acid (*Huckel,* Ann. **502,** 136):

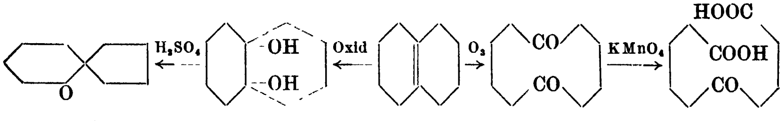


$\Delta^{1,9}$-Octalin Cyclohexanone-2-butyric acid m.p. 61° (*semicarbazone* m.p. 189°, *oxime* m.p. 103°) δ-Keto sebacic acid, m.p. 116° (*semicarbazone* m.p. 180°)

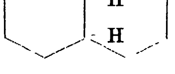
$\Delta^{1,9}$-Octalin is the simplest representative of a condensed ring system with a double bond attached to one of the branched carbon atoms. Its heat of combustion is normal, i.e., this position of the double bond at the branching implies no rise in energy content.

$\Delta^{9,10}$-Octalin (*$\Delta^{9,10}$-dicyclohexene*) (I), m.p. — 34°, b.p. 194–196°, arises from α- and β-decalol by the action of $KHSO_4$, naphthalene-sulphonic acid, or toluene-sulphonic acid; it is also obtained from trans o-cyclopentyl-cyclopentanol and $ZnCl_2$ at 140°. The 9, 10 position of the double bond is indicated by the formation of a blue solid *nitrosochloride* m.p. 91° (*Baeyer,* Ber. **27,** 454; Ann. **379,** 196 etc.), and is established beyond doubt by the facts, (1) that with ozone cyclodecane-dione (II) (p. 81) is obtained, which is further oxidised by $KMnO_4$ to δ-keto-sebacic acid (III) m.p. 116° (*semicarbazone,* m.p. 180°), and (2) that the diol (IV) $C_{10}H_{18}O_2$, m.p. 84–92° (*diacetate,* m.p. 169°) obtained by cautious oxidation, undergoes a pinacolin rearrangement into cyclohexanone-spiro-cyclopentane (V), *oxime* m.p. 64°:

V IV I II III

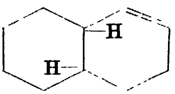


$\Delta^{1,2}$-Octalin cis,



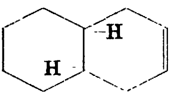
dibromide m.p. 61°, *nitrosochloride*, a colourless compound, m.p. 186°, is the main product of thermal decomposition of the xanthate of cis α-decalol, m.p. 93° (id. Ann. **502**, 144). It is also obtained, together with **$\Delta^{2,3}$-octalin** cis, by elimination of water from cis β-decalol, m.p. 105°, with $KHSO_4$ (*Leroux*, Ann. ch. phys. **21** (1910), 458). Oxidation of the mixture results in cis cyclohexane-propionic-carboxylic acid and cis cyclohexane-diacetic acid, indicating the presence of both octalins.

$\Delta^{1,2}$-Octalin trans,



b.p. 185°, blue liquid *nitrosochloride*, is prepared by the exhaustive methylation of trans α-decalyl-amine, m.p. —1°. Its constitution follows from the fact that oxidation yields trans cyclohexane-1-propionic-2-carboxylic acid, m.p. 143° (*Huckel*, Ann. **502**, 150).

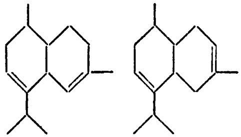
$\Delta^{2,3}$-Octalin trans,



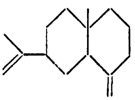
m.p. —21 to —24°, has been prepared from trans β-decalol, m.p. 75°, by elimination of water with $KHSO_4$, but is probably not a single substance. Oxidation yields trans cyclohexane-diacetic acid. *Dibromide*, m.p. 85°. (id. Ann. **451**, 148; **502**, 151.)

Hexalins (hexahydro-naphthalenes).—A hexalin $C_{10}H_{14}$, b.p. 200° is formed when naphthalene is heated with HI and P, together with octalins and decalins (*Agrestini*, Gazz. **12**, 495; *Graebe*, Ber. **16**, 3032; *Wreden*, Ann. **187**, 164). For the formation of hexalins from dichloro-decalin by boiling with aniline see *Borsche*, Ann. **434**, 222. *Hexahydronaphthols*, see *Nishimatsu*, C. 1928, I 2369.

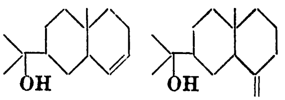
The following homologous unsaturated derivatives of the decalin ring system with 2 or 3 double bonds are of interest because of their occurrence in nature (see Sesquiterpenes p. 321):



α- and β-Cadinene



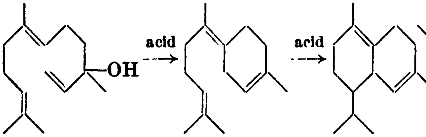
β-Selinene



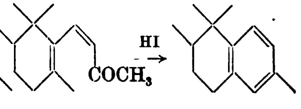
α- and β-Eudesmol

(*Ruzicka*, Helv. **7**, 84; **14**, 1132)

Bicyclic terpenes of this kind are readily obtained when the corresponding aliphatic or monocyclic unsaturated compounds are treated with inorganic acids (*Ruzicka*, Helv. **8**, 259; Ann. **468**, 134; *Tiemann*, Ber. **26**, 2675), e.g.



Nerolidol Bisabolene Zingiberene



Irone Irene.

Irene $C_{14}H_{20}$ (p. 128), *ac-1,1,2-trimethyl-ar-6-methyl-tetrahydro-naphthalene*[1], b.p. 119–123°/10 mm., d_4^{20} 0.935, from irone by boiling with HI and P

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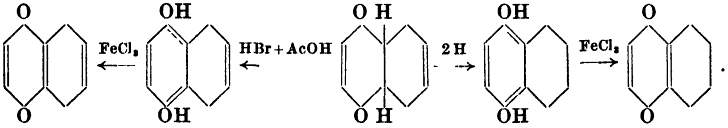
[1] *Ac* indicates substituents attached to the reduced alicyclic nucleus and *ar* to the unreduced aromatic nucleus.

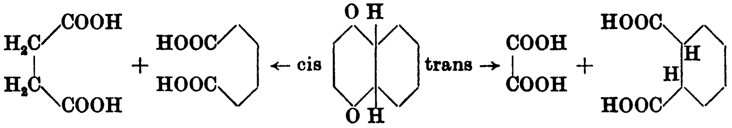
(*Tiemann*, Ber. **26**, 2675), gives 1,2,6-trimethyl-naphthalene when heated with Se (*Ruzicka*, Helv. **16**, 1143).

Butadiene-quinone adduct (I) $C_{10}H_{10}O_2$, pale yellow, m.p. 58°, can be reduced selectively, with enolisation of the quinone nucleus, to the hydroquinone (II), m.p. 185°; this is converted into the quinone (III), m.p. 57°, by $FeCl_3$. With HBr-AcOH butadiene-quinone undergoes isomeric change into an unsaturated hydroquinone (IV), m.p. 212°, which gives the unsaturated yellow quinone (V), m.p. 109° on treatment with $FeCl_3$ (*Diels*, Ber. **62**, 2345):

V IV I II III

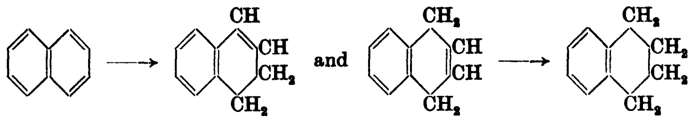


The tetrahydro compound of the original condensation product is known in a cis form, m.p. 50°, and in a trans form, m.p. 122°. Their constitution was established by oxidation with HNO_3 (*Alder*, Ann. **501**, 247), as is shown in the following scheme:



Succinic acid, anh. m.p. 121° Adipic acid, m.p. 152° Oxalic acid trans Hexahydrophthalic acid, m.p. 221°.

Next after compounds of this type, there are the partially hydrogenated naphthalenes, in which only one nucleus of the naphthalene system has been reduced, while the other nucleus retains its aromatic character. These naphthalene derivatives are noteworthy because they display, in one and the same substance, the differences between of an *aromatic* and a *hydroaromatic* or *alicyclic* nucleus. While the non-reduced nucleus has aromatic properties, the reduced alicyclic nucleus has those of an aliphatic compound, so that the two together give a compound which behaves like a homologue of benzene (*Bamberger*, Ann. **257**, 1):



Naphthalene Δ_1 Dihydro-naphthalene Δ_2 Tetralin.

These compounds will be described in the section dealing with naphthalene, vol. III.

CARBOXYLIC ACIDS OF THE DECALIN SERIES

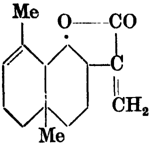
Some members of this series occur naturally as lactones, e.g. santonin, the alanto-lactones, etc.

Decalin-2-acetic-2-carboxylic acid, $C_{13}H_{20}O_4$, cis form m.p. 170°, (*anhydride* m.p. 94°), trans form m.p. 150° (*anhydride* m.p. 91°), is obtained from β-decalone-cyanhydrin and sodio-cyanacetic ester (*Hückel*, Ber. **59**, 2838).

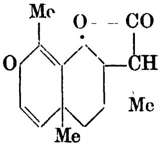
Decalin-1,1-diacetic acid $C_{14}H_{22}O_4$, trans acid m.p. 169° (*anhydride* m.p. 94°), from α-decalone and two molecules of cyanacetic ester.

Decalin-2,2-diacetic acid, cis m.p. 167°, trans m.p. 175°, by the same method from β-decalone (*Huckel*, ib.; *Rao*, J. **1929**, 1954).

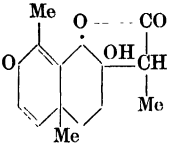
The natural lactones of the decalin series are described in detail in the section dealing with natural poisons (p. 486). This formulae are shown in the following summary:



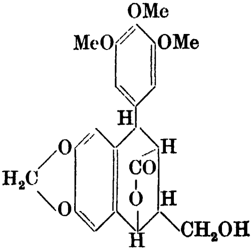
Alantolactone
(see p. 486)



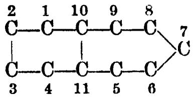
Santonin
(see p. 488)



Artemisin
(see p. 490)



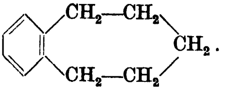
Podophyllotoxin
(see p. 493)



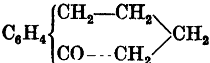
THE BICYCLO-[0,4,5]-UNDECANE SYSTEM

This system is only known in derivatives in which the six-membered ring is aromatic in character, i.e. derivatives of

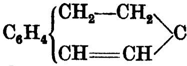
Benzo-cycloheptane



They will be discussed here because of their close relation to the preceding ring systems.



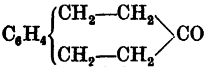
o-Benzo-cycloheptanone-2 $C_6H_4\left\{\begin{matrix}CH_2—CH_2\\CO--CH_2\end{matrix}\right\rangle CH_2$, b.p. 270°, is formed by internal condensation of δ-phenyl-valeric chloride with $AlCl_3$. The *oxime*, m.p. 109°, is reduced to benzo-α-amino-cycloheptane, the *hydrochloride* of which dissociates on heating into NH_4Cl and



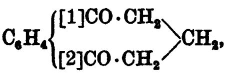
o-Benzo-Δ³-cycloheptene $C_6H_4\left\{\begin{matrix}CH_2—CH_2\\CH{=}CH\end{matrix}\right\rangle CH_2$, b.p. 234°. This latter compound is oxidised to o-phenylene-1-butyric-2-carboxylic acid (vol. III) (*Kipping, Hunter*, Proc. **19**, 11; J. **83**, 246). Reduction of benzo-cycloheptanone with amalgamated zinc gives the parent hydrocarbon:

o-Benzo-cycloheptane, b.p. 217° (*Borsche*, Ber. **54**, 174).

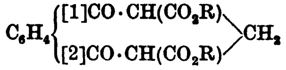
o-Benzo-cycloheptanone-4, *o-(pentanone-3-ylene)-benzene,*



$C_6H_4\left\{\begin{matrix}CH_2—CH_2\\CH_2—CH_2\end{matrix}\right\rangle CO$, m.p. 41—42°, obtained by distillation at 0·1 mm. Hg pressure of thorium o-phenylene-dipropionate, has a strong odour resembling that of peppermint and of bitter almonds (*Kubota* and *Isemura*, C. 1931 II 704).

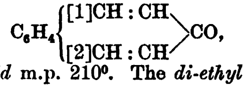


Benzo-cycloheptanedione-5,9 $C_6H_4\left\{\begin{matrix}[1]CO\cdot CH_2\diagdown \\ [2]CO\cdot CH_2\diagup\end{matrix}\right. CH_2$, m.p. 46° is obtained by ketonic hydrolysis of **phthalyl-glutaric ester**



$$C_6H_4\left\{\begin{matrix}[1]CO\cdot CH(CO_2R)\diagdown \\ [2]CO\cdot CH(CO_2R)\diagup\end{matrix}\right. CH_2$$

which is prepared by condensation of phthalic ester and glutaric ester by means of sodium ethoxide (*Dieckmann*, Ber. **32**, 2227).



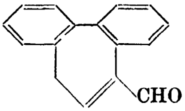
Benzo-cycloheptane-dienone $C_6H_4\left\{\begin{matrix}[1]CH:CH\diagdown \\ [2]CH:CH\diagup\end{matrix}\right. CO$, m.p. 67°, is prepared from its *dicarboxylic acid* m.p. 210°. The *di-ethyl ester* of this acid, m.p. 95°, results from the condensation of o-phthalic aldehyde with acetone-dicarboxylic ester in presence of di-ethylamine. *Homologues of benzo-cycloheptadienone* are formed when o-phthalic aldehyde is condensed with methyl-ethyl-ketone, diethyl-ketone, dibenzyl-ketone, etc., together with *acyl-hydrindones*. They are reduced by sodium and alcohol to the corresponding *benzo-cycloheptanols* (*Thiele*, Ann. **377**, 1).

Hydrolysis of diphenylene-2,2′-diacetaldehyde acetal does not give a dialdehyde, as might be expected, but ring closure takes place and

Dibenzo-cycloheptene-aldehyde (I) is formed (*Weitzenbock*, Mo. **34**, 193).

Cyano-imido-dibenzo-cycloheptane (II) is formed by the similar ring closure of 2,2′-dicyano-methyl-diphenyl in presence of NaOEt (*Kenner*, J. **99**, 2101):

I



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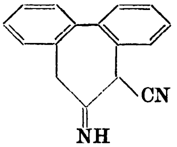
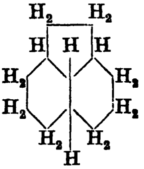
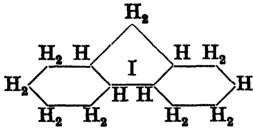
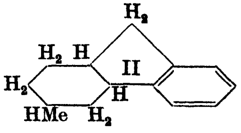


HIGHLY CONDENSED ALICYCLIC COMPOUNDS



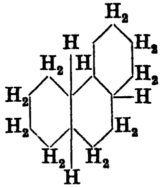
Acenaphthene-per-(deca-)hydride, $C_{12}H_{20}$, b.p. 235–236°, is obtained from acenaphthene with HI and P (*Liebermann*, Ber. **22**, 781) or with H_2 and Ni (*Ipatiev*, Ber. **42**, 2094).



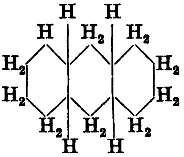


Fluorene-per-(dodeca-)hydride (I) $C_{13}H_{22}$, b.p. 254–258°, is prepared from fluorene with HI and P (*Liebermann*, l. c.; *Spiegel*, Ber. **41**, 885; *Ipatiev*, l. c.).

Hexahydro-methyl-fluorene (II) $C_{14}H_{18}$, b.p. 128°/14 mm., is formed from 2-benzyl-5-methyl-hexanol-1 by ring closure with P_2O_5 (*Wallach*, Ber. **29**, 2962).



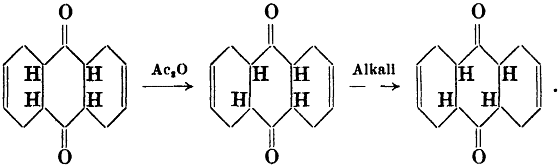
Phenanthrene-per-(tetradeca-)hydride $C_{14}H_{24}$, b.p. 270–275°, is obtained by energetic hydrogenation of phenanthrene by HI + P. It is doubtful whether the product is homogeneous (*Liebermann, Spiegel*, ll. cc.; *Ipatiev*, Ber. **41**, 884, 1000). Partially reduced phenanthrenes are mentioned at the end of the section on phenanthrene (vol. III).



Anthracene-per-(tetradeca-)hydride $C_{14}H_{24}$, m.p. 89°, is obtained from anthracene by complete reduction with HI + P (*Lucas*, Ber. **21**, 2510; *Ipatiev*, l. c.).

Partially reduced anthracenes, see anthracene, vol. III.

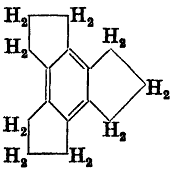
Bis-butadiene-quinone, $C_{14}H_{16}O_2$, a colourless compound, is obtained by protracted heating of benzoquinone with an excess of butadiene in a sealed tube. The product itself and its tetrahydro derivative can be converted in stages from the cis-cis to the trans-trans form:



(a) m.p. 155° (b) m.p. 186° (c) m.p. 244°

The configurations of the compounds have been established by oxidising the a-form to cis hexahydro-phthalic acid m.p. 192° and adipic acid m.p. 152°, and the b- and c-forms to trans hexahydro-phthalic acid m.p. 220° and adipic acid (*Alder*, Ann. **501**, 255).

I



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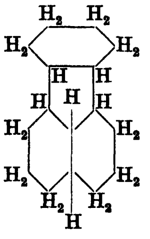

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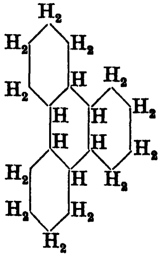
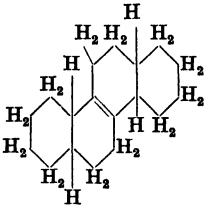


Tricyclo-trimethylene-benzene (I) $C_{15}H_{18}$ m.p. 97° is obtained by the condensation of cyclopentanone by means of gaseous HCl (*Wallach*, Ber. **30**, 1096).

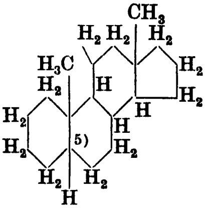
Perhydro-fluoranthene (II) $C_{16}H_{26}$, m.p. 75°, b.p. 168–170°/12 mm. from fluoranthene (vol. III) with Ni and hydrogen (*v. Braun*, Ber. **68**, 2610).

Perhydro-triphenylene (III) $C_{18}H_{30}$ b.p. 175–176°/7 mm. is prepared by condensing o-cyclohexyl-cyclohexanol with phenol and hydrogenating the resulting bicyclohexyl-phenol, with subsequent ring closure and reduction (*v. Braun*, Ber. **56**, 2024).

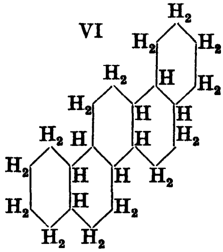
IV



V



VI



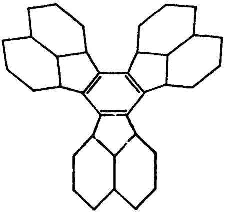
Hexadecahydro-chrysene (IV), $C_{18}H_{28}$, b.p. 168°/0·5 mm. (id. Ber. **65**, 883) is the product of complete hydrogenation of chrysene.

The graphical formula (V) represents a complicated tetracyclic ring system which is contained in several groups of substances of biological importance, e.g. the sterols, bile acids, sex hormones, toad poisons and the vegetable heart poisons of the digitalis series. Cf. the sections on sterols and cholic acids, poisons, vitamins, hormones. The sterols and bile acids are derived from two hydrocarbons corresponding to formula (V), which are stereoisomeric in the arrangement about C_5:

Etiocholane, $C_{19}H_{32}$, m.p. 80°, and **allo-etiocholane,** m.p. 50°; the latter is identical with *androstane*, p. 590 (*Butenandt*, Z. pnysiol. Ch. **229**, 190, 208).

Hydro-picene (VI), $C_{22}H_{36}$, m.p. 175°, from picene by the action of HI and P at 250° (*Bamberger*, Ber. **26**, 1751).

Trisdecahydro-decacyclene, $C_{36}H_{48}$, m.p. 215°, is formed when decacyclene $C_{36}H_{18}$ is catalytically reduced with nickel at a pressure of 200 atm. Oxidation of this hydrocarbon with conc. HNO_3 gives mellitic acid (*v. Braun*, Ber. **67**, 214).



Other condensed systems of this kind are referred to in the section dealing with condensed aromatic compounds in vol. III.

4. RING SYSTEMS WITH BRIDGED MEMBERS

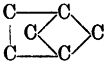
The first compound which was recognised as belonging to this class was camphor; afterwards pinene, fenchone, santene and many other natural products were found to contain bridged ring systems. Because of their importance they are discussed in a separate chapter, "The Bicyclic Terpene Group" (p. 239), together with their derivatives and products of reaction.

In bridged rings three or more carbons are common to two rings. These ring systems can be regarded as consisting of a five-, six-, or seven-membered ring, etc., in which two non-adjacent carbon atoms (the "bridge heads") are joined by a bridge of one, two or more carbon atoms (*Bredt*, *Savelsberg*, J. pr. **97**, 1). *Bredt* introduced the term "*meso*" for the members of the bridge (Ann. **292**, 124), while *Diels* calls them "*endo*" (ib. **460**, 99). Accordingly one uses the terms mesomethylene or endomethylene, and mesoethylene or endoethylene compounds, for compounds which contain one- or two-membered bridges. Compounds with more than two C-atoms in the bridge are not yet known.

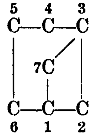
Bridged rings are also known, which contain a bridge of one C and one O-atom, as in 1,8-cineole, one O-atom alone, as in 1,4-cineole, and two O-atoms, as in ascaridole. Nitrogen also occurs as a bridged member, as in the tropane compounds (vol. IV), and has been termed *meso*-N by *Willstätter*.

The following ring systems are examples of bridged rings. Of the many systems of nomenclature which have been suggested for these compounds, the names used by *Baeyer*, *Bredt* and *Diels* have been adopted (see *Beilstein*, IV. Aufl., Bd. V, p. 13–14).

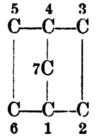
Bicyclo-[1,1,2]-hexane, *1,3-mesomethylene-cyclopentane.* This carbon skeleton was one time thought to exist in derivatives of camphor (the old camphenilone formula), but this view had to be abandoned later in favour of the bicyclo-[1,2,2]-heptane system. It is questionable whether this ring system can exist, because of the great strain.



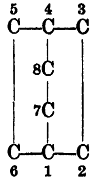
Bicyclo-[1,1,3]-heptane, *1,3- (or m-) mesomethylene-cyclohexane,* **Norpinane.** Pinene is the most important representative of this type.



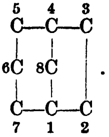
Bicyclo-[1,2,2]-heptane, *1,4- (or p-)-mesomethylene-cyclohexane,* **Norcamphane,** the ring system of the camphane group.



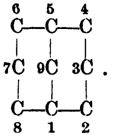
Bicyclo-[2,2,2]-octane = *1,4-endoethylene-cyclohexane.* Compounds of this group can be obtained synthetically by means of the *Diels-Alder* diene synthesis (see below).



Bicyclo-[1,2,3-]octane, *1,4-mesomethylene-cycloheptane,* **Homonorcamphane.** Compounds of this group have been obtained synthetically from the camphane system by ring enlargement. They have also been prepared by distillation of the Pb- or Ca-salts of the homologues of camphoric acids (see general methods of preparation).



Bicyclo-[1,3,3]-nonane, *1,5-mesomethylene-cyclo-octane.* Compounds made from cyclohexenone and β-keto-esters by *Rabe's* method, and from malonic acid and aldehydes by *Meerwein's* method contain this carbon skeleton.



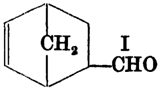
Of the General Methods of Synthesis which give bridged rings the following should be mentioned:

I. Condensation of the esters and thermal decomposition of the salts of cyclic 1,3-carboxylic-acetic acids or of 1,3-carboxylic-propionic acids with suitable substituents. Cyclobutane compounds give the bicyclo-[1,1,3]-heptane system, and cyclopentane derivatives the bicyclo-[1,2,2]-heptane or the bicyclo-[1,2,3]-octane system. Examples of this method are the syntheses of the following: pinene (*Ruzicka*), camphor (*Bredt-Haller*; the first synthesis of this kind); fenchone (*Ruzicka*); norcamphor (*Komppa*); homocamphor (*Lapworth*).

II. The *Diels-Alder* diene synthesis can lead to (a) bicyclo-[1,2,2]-heptanes and also (b) bicyclo-[2,2,2]-octanes, as will be seen from the following examples:

a) Cyclopentadiene is condensed with acrolein to (I), or with acetylene-dicarboxylic ester to (II), or dimethyl-fulvene is condensed with maleic anhydride to (III). Cyclopentadiene on polymerisation gives (IV) and (V), and when condensed with quinone gives (VI) and (VII).

b) Cyclohexadiene condenses with maleic anhydride to (VIII) and dimerises to (IX). Anthracene condenses with maleic anhydride to (X).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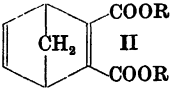
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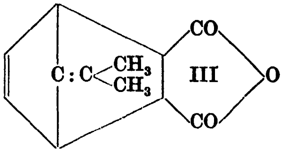
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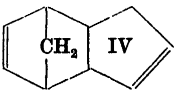
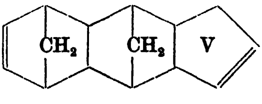
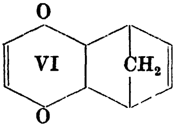
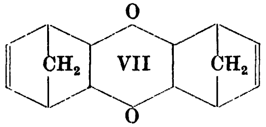
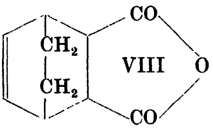
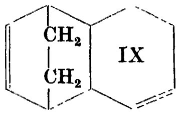

IV

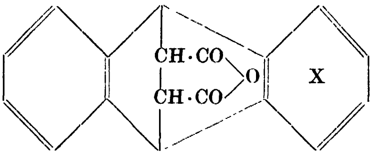

V





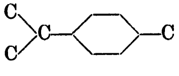




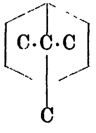


GENERAL PROPERTIES.

Bicyclic ring systems in which the molecule extends roughly the same amount in the three dimensions of space, and so has a more or less spherical shape, such as camphor, pinene dibromide, bicyclopentadiene, tricyclene, are distinguished by an extraordinarily high value for the molecular lowering of the freezing point (E = 30—80°). Compounds in which the molecule is elongated, so that there is no approximation to spherical shape, like tricyclopentadiene, have much lower constants, *E* = 8—12° (*Pirsch,* Ber. **65**, 662; **66**, 815, 1694; **67**, 101, 373). The ratio of the molecular depression constant E to the molecular weight M has been found to be a constant characteristic for each ring system. The values for cyclohexanes and for bicyclo-[1,2,2]-heptanes e.g. are (id. Ber. **65**, 1839):

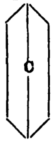
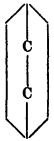
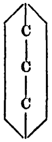
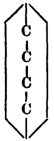


$\frac{E}{M} = 0{\cdot}043,$



$\frac{E}{M} = 0{\cdot}26.$

The strains existing in bridged cycloparaffin rings are illustrated by the following comparison (*Hückel,* Ann. **455**, 123):

Bicyclo-[1,2,2]-heptane	Bicyclo-[2,2,2]-octane	Bicyclo-[3,2,2]-nonane	Bicyclo-[4,2,2]-decane
			
calculated 77°22′	practically strainless	strain somewhat less than in 4-membered bridge	calculated 38°56′

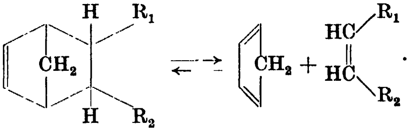
Correspondingly, the heat of combustion of camphor is 8—9 kcal/mol higher than that of the isomeric cis-β-decalone, which is free from strain (*Roth*, Ber. **46**, 313; Ann. **441**, 48), and the heat of combustion of the strained bicyclo-[1,2,2]-heptane ring (tetrahydro-dicyclopentadiene, norcamphor) is 6—7 kcal/mol higher than that of the strainless bicyclo-[2,2,2]-octane ring (tetrahydro-dicyclohexadiene, endoethylene-cyclohexanone).

Just as the cis forms of bicyclic hydroaromatic compounds are 2—5 kcal/mol higher in energy content than the corresponding trans forms, equally so the energy content of the α-series of the compounds of bicyclo-[1,2,2]-heptanes (polymeric cyclopentadienes) is greater than this of the corresponding compounds of the β-series by 2—3 kcal/mol. In bicyclo-[1,2,2]-heptenes, because of the strain caused by a bridge which contains only one member, the heat of hydrogenation (dicyclopentadiene, 33·2 kcal) is greater than in the straight-chain olefins (ethylene 32·58 kcal), the semicyclic olefins (methylene-cyclohexane, 25 kcal), and the cyclic olefins (cyclohexene 28·59 kcal). (*Alder*, Ber. **67**, 613; *Becker*, ib. p. 627; *Kistiakowsky* et al., Am. **57**, 65, 876; **58**, 137, 146).

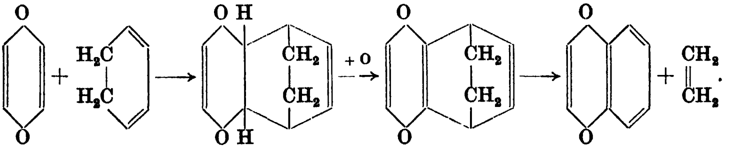
The introduction of a carbon bridge into the ring causes a certain rigidity of both cis and trans derivatives. Trans bicyclo-[1,2,2]-heptane-dicarboxylic and trans bicyclo-[2,2,2]-octane-dicarboxylic acids are both unable to form anhydrides (*Diels*, Ann. **478**, 142).

Bredt's rule (*Wüllner*-Festschrift Leipzig 1905; J. pr. Ch. **97**, 1: Ann. **437**, 1; *Windaus*, ib. **442**, 7; cf. p. 270) states that the bicyclo-[1,1,3]- and bicyclo-[1,2,2]-heptane compounds with a double bond at one of the carbons atoms forming a bridge head cannot exist.

As to the stability of the bridged rings it should be noticed that the saturated bicyclo-[1,2,2]-heptanes with a cyclopentane ring are completely stable to catalytic dehydrogenation (*Zelinsky*, Ber. **56**, 1716; **66**, 1415), while in the bicyclo-[1,1,3]-heptanes with a cyclobutane ring one of the rings is opened (id. Ann. **476**, 60). The former compounds are quite stable to heat, while bicyclo-[1,2,2]-heptene derivatives disintegrate into their components either when heated or treated with platinum catalysts:



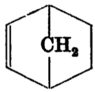
A different mode of thermal decomposition is found in the endoethylene compounds obtained by oxidising the condensation products of quinones with cyclohexadienes. The ethylene bridge is destroyed and an aromatic system formed:



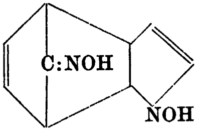
The reaction is important for the determination of constitution.

A specific reaction of the bicyclo-[1,2,2]-heptene ring system (e.g. (I), (II), (III), the *endoxohexene* system (IV) and the *endomethylene-azine* system (V)

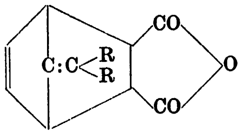
I



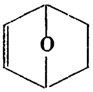
II



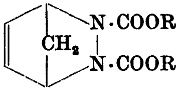
III



IV

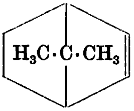


V

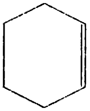


consists in their ability to combine additively with *azides* (phenyl azide, benzyl azide, benzoyl azide) and *diazo compounds* (diazomethane, diazo-acetic ester), dihydro-triazoles and pyrazole derivatives being formed (*Thiele*, Ann. **394**, 68; *Alder*, ib. **484**, 243; **501**, 1; *Diels*, ib. **490**, 243). Compounds with a dimethyl-methylene bridge (I), cyclohexene (II), and compounds with an ethylene bridge (III) are exceptions; these do not react at all, or only slowly:

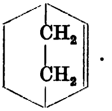
I



II



III

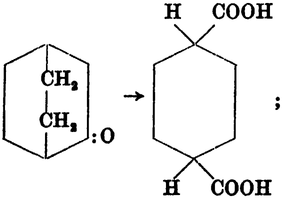


The action of *hydrogen* and that of *nitrosyl chloride* are just as selective as the condensation with the above nitrogen compounds; oxygen, on the other hand, e.g. in the action of per-acids, attacks the double bonds unspecifically (*Alder*, Ann. **485**, 234).

Bromination of these particularly reactive unsaturated bicyclic systems takes place abnormally and forms hydroxybromides (*Alder*, Ann. **501**, 253; **504**, 230).

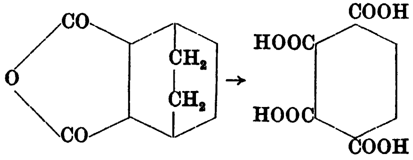
Bicyclo-[1,2,2]-heptenes can take part in *further diene addition* (cf. the formation of tri- and tetracyclopentadiene [*Alder*, Ann. **496**, 218]), while cyclohexenes and bicyclo-[2,2,2]-octenes cannot do so.

The nature of a bridged ring system can be ascertained by examining its oxidation products. A bicyclo-[1,1,3]-heptane ring gives *cyclobutane* derivatives as the primary products of reaction. The degradation of α-pinene, for instance, gives pinoyl-formic acid together with pinonic, pinic and norpinic acids, p. 253. From bicyclo-[1,2,2]-heptane compounds *cyclopentane* carboxylic acids are first obtained, see the campha negroup p. 262. Bicyclo-[2,2,2]-octanes (endoethylene compounds) are converted into hexahydroterephthalic acids by conc. HNO_3 (*Diels*, Ann. **478**, 137; Ber. **62**, 2087);



cis-Hexahydroterephthalic acid

;



Hexahydro-
mellophanic acid.

The other types of ring fission and of isomeric change which have been observed in the bicyclo-[1,1,3]-heptane and the bicyclo-[1,2,2]-heptane systems are described in the sections dealing with pinane and camphane derivatives.

For the *nomenclature* of bridged ring systems *Baeyer's* rules (p. 161) may be applied with advantage, or they may be called meso or endo alkylene compounds, as suggested by *Bredt* and by *Diels*. The numbering of the ring carbon atoms used in this book begins at one of the two bridge heads, continues round the smaller ring, if the bicyclic system is unsymmetrical, and ends with the bridging members. *Diels* prefers to start from the point of attachment of some functional group. In the terpenes, the names are sometimes based on genetic relationships.

BICYCLO-[1,1,3]-HEPTANES

Bicyclo-[1,1,3]-heptane or "*norpinane*" is the parent substance of important natural products, such as α- and **β-pinene, verbenone** etc. which will be described in detail in the section "the pinane group" of the chapter on Terpenes. The **caryophyllenes** (cf. Sesquiterpenes p. 329) are held to be derivatives of this ring system. The filix tannins are also derived from bicyclo-1,1,3-heptane (see Tannins, p. 398).

BICYCLO-[1,2,2]-HEPTANES

The carbon skeleton of bicyclo-[1,2,2]-heptane or "*norcamphane*" is contained in a large number of natural products, hydrocarbons, alcohols and ketones, and the group is called "the camphor group", after the most important of them. Camphor, its reactions and degradation products, its isomers, and its lower and higher homologues are fully described unter the heading "camphane group" in the chapter on Terpenes. Only the artificial products, obtained by means of the *Diels-Alder* synthesis (p. 86) will be discussed here in detail.

Bicyclo-[1,2,2]-heptane, "*norcamphane*", Komppa's "*norbornylane*", the parent hydrocarbon of the group, is a very volatile substance, m.p. 86–87°. It has been obtained by a *Hofmann* degradation of bicyclo-[1,2,2]-heptanecarboxylic amide, deamination to β-norborneol and reduction of the corresponding chloride with sodium and alcohol (*Komppa*, Naturwiss. **22**, 171).

2-Methyl-bicyclo-[1,2,2]-heptane, *2-methyl-1,4-endomethylene-cyclohexane,* C_8H_{14}, b.p. 125–126·5°. Cyclopentadiene is condensed with acrolein (*Diels*, Ann. **460**, 98) to endomethylene-tetrahydro-benzaldehyde (p. 186), which is reduced via the hydrazone to endomethylene-tetrahydrotoluene, b.p. 115–117°, and finally reduced with hydrogen and palladium (*Zelinsky*, Ber. **66**, 1415).

2-Methylene-bicyclo-[1,2,2]-heptene, *2-methylene-norcamphane,* C_8H_{12}, b.p. 123°, arises from the same cyclopentadiene-acrolein compound by the stages endomethylene-hexahydrobenzaldehyde (p. 186) and endomethylene-hexahydrobenzylalcohol (see below) (*Diels*, Ann. **470**, 62).

Santene, *2,3-dimethyl-1,4-endomethylene-cyclohexene-2,* C_9H_{14}, b.p. 137–140°, is prepared similarly by means of the diene synthesis from norcamphor (p. 270, Terpenes).

Among the higher homologous hydrocarbons of this series, the isomers $C_{10}H_{18}$,

Camphane and **Fenchane** are noteworthy as the parent substances of important natural products. For the proof of their constitution and the numerous rearrangements of these ring systems see Terpenes, p. 263 and 271.

Alcohols

Bicyclo-[1,2,2]-heptane-carbinol-2, *norcamphane-2-carbinol, 1,4-endomethylene-hexahydrobenzyl alcohol-2,* $C_8H_{14}O$, b.p. 101–102°/10 mm., has been

prepared by reducing the condensation product of cyclopentadiene and acrolein p. 181 (*Diels*, Ann. **470**, 62).

Borneol, its isomer **isoborneol** and **fenchyl alcohol** are homologous compounds occurring in nature and are dealt with in the chapter on Terpenes.

Bicyclo-[1,2,2]-heptene Aldehydes

can in general be obtained from cyclopentadiene and α, β-unsaturated aldehydes. The following adducts are derived from acrylic and crotonic aldehydes:

1,4-Endomethylene-Δ^5-tetrahydro-benzaldehyde-2, $C_8H_{10}O$, b.p. 70–72°/20 mm., *semicarbazone* m.p. 162°, is hydrogenated to *endomethylene-hexahydrobenzaldehyde* (norcamphane-2-aldehyde), b.p. 75–76°/25 mm., *semicarbazone*, m.p. 142° (*Diels*, Ann. **460**, 98; **470**, 62; **486**, 202).

1,4-Endomethylene-methyl-Δ^5-tetrahydro-benzaldehyde-2, $C_9H_{12}O$, cis form b.p. 60–75°/12 mm., *semicarbazone* m.p. 158°, and trans form b.p. 80°/45 mm., *semicarbazone* m.p. 181°; on oxidation the dihydro-products give cis and trans *endomethylene-hexahydro-o-toluic acid*, see below (*Diels*, Ann. **470**, 66).

Cyclic Ketones

can prepared not only by the older methods of *Komppa* and *Bredt-Haller* (p. 181), but also by ozonising the enol acetates of bicyclo-[1,2,2]-heptane-aldehydes.

Norcamphor, *1,4-endomethylene-cyclohexanone-2,* $C_7H_{10}O$, m.p. 92°, *semicarbazone* m.p. 197° (*Diels*, Ann. **470**, 62), and

3-Methyl-norcamphor, *1,4-endomethylene-3-methyl-cyclohexanone-2,* b.p. 68–70°/15 mm., *semicarbazone* m.p. 185°. Both these ketones are important intermediate stages in the complete synthesis of santene (p. 270) and of **camphor** by the diene method (see Terpenes; *Diels*, Ann. **486**, 202). Camphor is treated in detail in the chapter on Terpenes (p. 282).

Fenchone isomeric with camphor also occurs in nature. For its constitution, ring fissions and synthesis see Terpenes (p. 315).

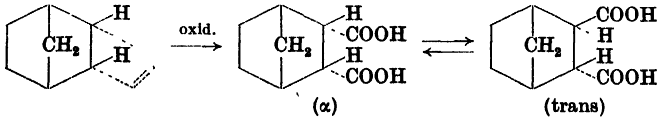
Carboxylic Acids

of the bicyclo-[1,2,2]-heptane class have been prepared by the same method of diene synthesis, starting from cyclopentadiene and α,β-unsaturated carboxylic esters or dicarboxylic anhydrides.

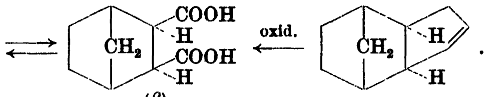
1,4-Endomethylene-Δ^5-tetrahydrobenzoic acid-2, $C_8H_{10}O_2$, b.p. 132–134°/22 mm., a compound which recalls the higher fatty acids in odour, has been obtained by condensing cyclopentadiene with acrylic acid (*Diels*, Ann. **460**, 98).

1,4-Endomethylene-hexahydro-2,3-toluic acid, $C_9H_{14}O_2$, exists in two isomeric forms, cis, b.p. 136–137°/13 mm., trans, m.p. 66°, and is prepared by oxidation of the corresponding aldehydes (*Diels*, Ann. **470**, 66).

1,4-Endomethylene-hexahydro-2,3-phthalic acids, $C_9H_{12}O_4$. Three isomers are known, two of them cis forms, α, m.p. 161°, *anhydride* m.p. 168°, and β, m.p. 153°, *anhydride* m.p. 79°, which can be converted into one another by way of the trans form, m.p. 194° (*Diels*, Ann. **460**, 113). The two cis forms are prepared by SeO_2-oxidation of α- and β-dihydro-dicyclopentadienes (*Alder*, Ann. **504**, 219):



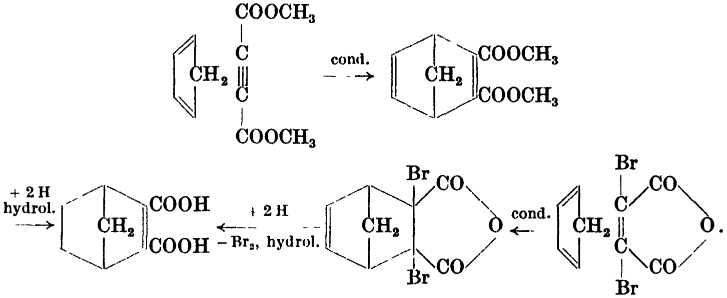
(α) (trans)



(β)

1,4-Endomethylene-Δ^5-tetrahydro-2,3-phthalic acids, $C_9H_{10}O_4$, display a similar isomerism: α-form m.p. 179°, *anhydride* m.p. 164°, β-form m.p. 148°, *anhydride,* m.p. 143°. The *dibromide* of the α-form, m.p. 188°, is transformed by HBr and acetic acid into the *dibromide* of the trans-acid, m.p. 244°, which does not form an anhydride; the trans-dibromide rearranges, when melted, to the *β-dibromide,* m.p. 248° (*Alder,* Ann. **504,** 224). The α-acid is synthesised by heating maleic anhydride with cyclopentadiene and hydrolysing the anhydride, m.p. 165°, of the condensation product (*Diels,* Ann. **460,** 98). Hydrogen and Pd reduce it to the corresponding saturated cis α-acid, m.p. 161°.

1,4-Endomethylene-Δ^2-tetrahydro-2,3-phthalic acid, m.p. 22°, differs from the previous acid in the position of the double bond. *Anhydride* m.p. 99°, *dimethyl ester* b.p. 132–133°/12 mm. It can be synthesised by the diene method in two ways which are shown in the scheme (*Diels,* Ann. **478,** 137):



Ozone attacks the Δ^1-double bond, and gives cis cyclopentane-1,3-dicarboxylic acid. The cyclopentadiene-acetylene-dicarboxylic ester adduct represented above, b.p. 134–135°/11 mm., gives on hydrolysis.

1,4-Endomethylene-$\Delta^{2,5}$-dihydro-2,3-phthalic acid, $C_9H_8O_4$, m.p. 170° (*Alder,* Ann. **490,** 236).

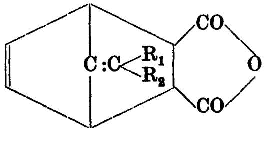
3-Methyl-1,4-endomethylene-Δ^5-tetrahydro-2,3-phthalic anhydride, $C_{10}H_{10}O_3$, m.p. 138°, is prepared from cyclopentadiene and citraconic anhydride.

1,4-Endomethylene-Δ^5-tetrahydrobenzene-2-carboxylic-2-acetic anhydride, an isomer of the previous compound, m.p. 54°, is obtained similarly from itaconic anhydride (*Diels,* Ann. **460,** 98).

1,4-Endomethylene-hexahydro-2,3-homophthalic acid, $C_{10}H_{14}O_4$, m.p. 137°, results from the degradation of dihydro-dicyclopentadiene with $KMnO_4$ (*Diels,* Ann. **485,** 223).

2,3-Dimethyl-1,4-endomethylene-Δ^5-tetrahydro-2,3-phthalic anhydride, $C_{12}H_{12}O_3$, m.p. 155°, is a condensation product of cyclopentadiene and pyrocinchonic anhydride (*Diels,* Ber. **62,** 554).

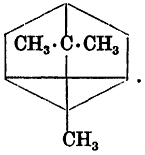
Addition of maleic anhydride to 6,6-substituted fulvenes results in compounds of the general formula:



Dimethyl derivative $C_{12}H_{12}O_3$, m.p. 137°
Diphenyl derivative $C_{22}H_{16}O_3$, m.p. 168°
Monostyryl derivative $C_{18}H_{14}O_3$, m.p. 138°.

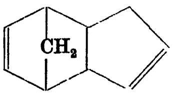
The constitution of these compounds is deduced from the facts: (1) that they can add on azides, and (2) that the diphenyl compounds give benzophenone on ozonisation (*Diels*, Ber. **62**, 2081).

The ring system of tricyclene (p. 275) which is of great theoretical interest, may be briefly mentioned here. It is a combination of a bicyclo-[1,2,2]-heptane and a condensed 3- and 5-ring system. Interesting natural substances, such as **α-santalene** (p. 333) and **teresantalic acid** (p. 270), described in the chapter on Terpenes, are derived from this system.

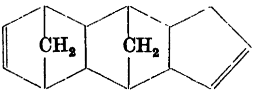


Polymerisation Products of Cyclopentadiene

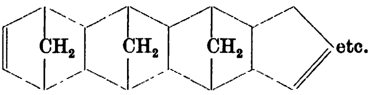
The polymerisation of cyclopentadiene takes place as in a diene synthesis and leads to the following products (*Kraemer*, Ber. **29**, 558; *Wieland*, Ber. **39**, 1492; id. Ann. **446**, 13; *Staudinger*, Helv. **7**, 23 etc.; *Alder*, *Stein*, Ann. **485**, 223; *Wassermann*, J. **1936**, 1028):



Dicyclopentadiene

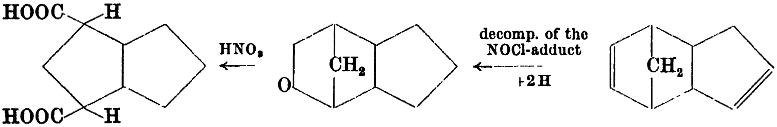


Tricyclopentadiene



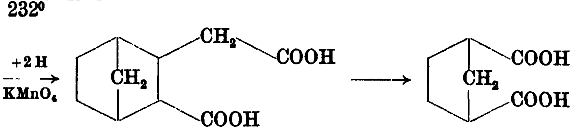
Tetracyclopentadiene.

Dicyclopentadiene, $C_{10}H_{12}$, α-form m.p. 32°, β-form m.p. 19°. This doubly unsaturated, tricyclic hydrocarbon contains two double bonds which are dissimilar, as can be seen by reduction. The *dihydro compound* melts at 51°, the *tetrahydro compound* at 77°. One double bond is capable of adding phenyl azide and of reacting with nitrosyl chloride, so that the compound must belong to the bicyclo-[1,2,2]-heptene group. The ring structure of the polymer has been established by oxidation; there are two possible points of attack, which can be shown as follows (*Wieland*, Ann. **446**, 20; *Ruzicka*, ib. **476**, 76; *Alder*, *Stein*, ib. **485**, 223):



cis-Pentalane-1,3-dicarboxylic acid $C_{10}H_{14}O_4$ m.p. 232°

Ring ketone m.p. 110°

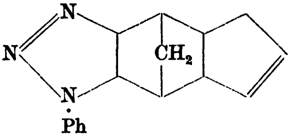


1,4-Endomethylene-hexahydro-2,3-homophthalic acid $C_{10}H_{14}O_4$, m.p. 137°

Cyclopentane-1,3-dicarboxylic acid $C_7H_{10}O_4$, m.p. 120°

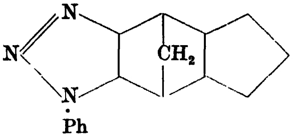
An exact examination of the stereochemical behaviour has shown that the two forms of dicyclopentadiene are stereoisomers and the difference persists in the following derivatives (*Alder*, Ann. **504**, 219):

Hydrotriazoles



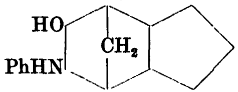
α-series m.p. 128°
β-series m.p. 128°

Dihydro compounds



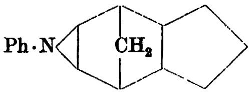
m.p. 129°
m.p. 142°

Hydroxy base



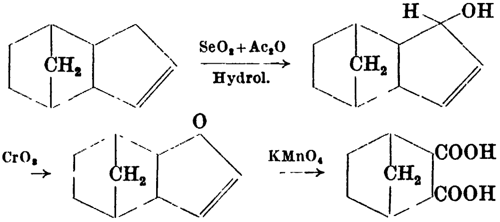
α-series m.p. 134°
β-series m.p. 95°

Ethylenimine

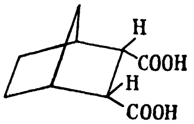


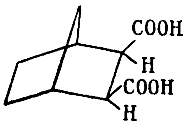
m.p. 62°
m.p. 68°

Oxidation of the α- and β-dihydro-dicyclopentadienes by the method described below (p. 190) gives rise to two isomeric cis 1,4-endomethylene-hexahydro-2,3-phthalic acids, m.ps. 161° and 153° (p. 186):

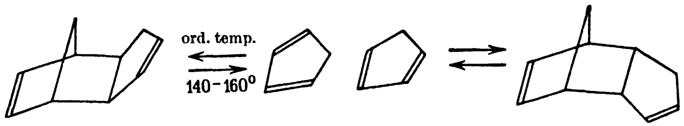


This can only be interpreted stereochemically by the view that the formulae of the acids are:

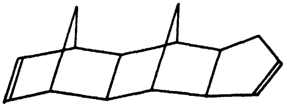


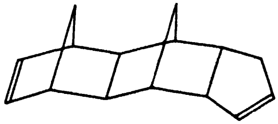


The polymerisation process itself can therefore be represented as:

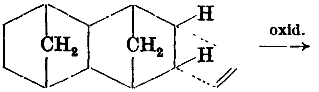


Two **tricyclopentadienes,** $C_{15}H_{18}$ are known and are obtained, together with still higher condensation products, by heating cyclopentadiene to 150–180° under high pressure; m.ps. 68° and 65°, *dihydro-triazoles* m.ps. 200° and 196°. It has been shown that they differ in a way similar to the dicyclopentadienes, and that their formulae must be (*Staudinger*, Ann. **447**, 99; *Alder*, ib. **496**, 204; **504**, 216):

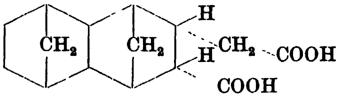




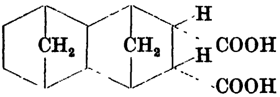
A successive degradation of the complicated ring system has been achieved by using the action of various oxidising agents on the dihydro compounds. Here again, two series of stereo-isomeric degradation products result, e.g. from α-tricyclo-pentadiene:



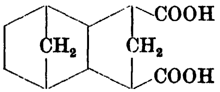
α-Dihydro-tricyclopentadiene, m.p. 36°



Acid $C_{15}H_{20}O_4$, m.p. 183°



Acid $C_{14}H_{18}O_4$, m.p. 174°

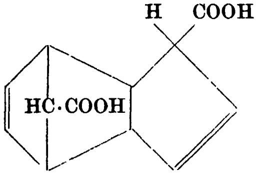


common oxidation product, acid $C_{12}H_{16}O_4$, m.p. 217°

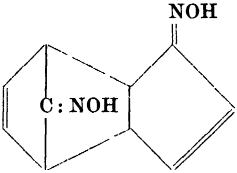
Tetracyclopentadiene, $C_{20}H_{24}$ m.p. 207°, *dihydro compound* m.p. 205°,
Pentacyclopentadiene, $C_{25}H_{30}$ m.p. 277°, and
Hexacyclopentadiene, $C_{30}H_{36}$ m.p. 373° decomp., are formed to some extent when dicyclopentadiene is heated to 200° for 90 hours (*Alder*, Ann. **496**, 204; Ber. **67**, 613: *Staudinger*, Ann. **447**, 97).

For the *energy content* of polymeric cyclopentadienes see p. 183; cf. *Alder*, Ber. **67**, 613.

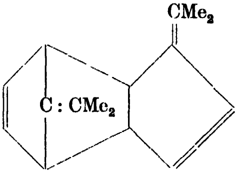
Dimerisation products of certain *cyclopentadiene derivatives* are known, e.g.



Dicyclopentadiene-dicarboxylic Acid
(*Thiele*, Ber. **34**, 69; *Alder*, Ann. **496**, 204).



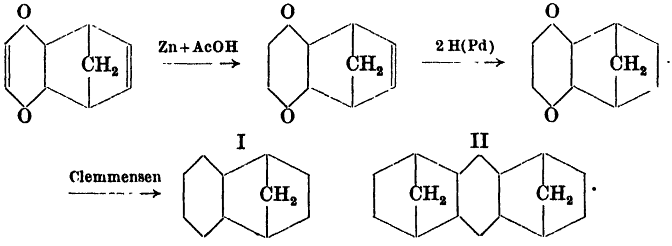
Di-isonitroso-dicyclopentadiene
(*Thiele*, Ber. **33**, 669; *Alder*, l. c.)



Di-dimethylfulvene
(*Thiele*, Ann. **348**, 7; *Alder*, l. c.)

1,4-Endomethylene-decalins and -tetradecahydro-anthracenes

1,4-Endomethylene-decalin (I), $C_{11}H_{18}$, b.p. 84–85°/15 mm., has been obtained from the cyclopentadiene-quinone adduct (cf. below) by reduction in the following stages (*Walther*, Ann. **348**, 47; *Diels*, Ann. **460**, 98):

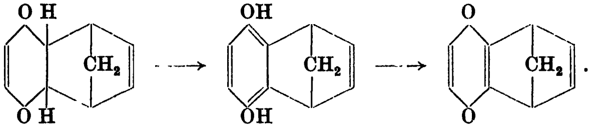


I

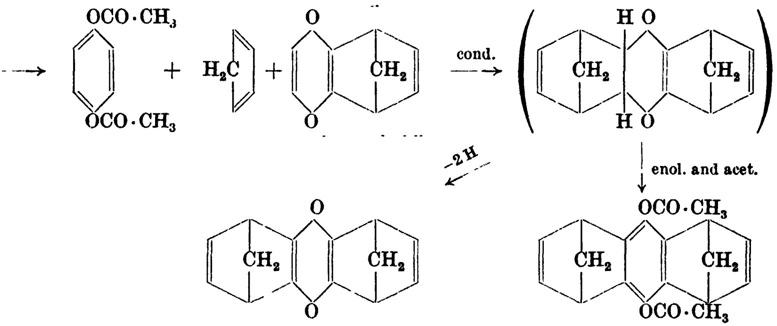
II

1,4,5,8-Di-endomethylene-tetradecahydro-anthracene (II), $C_{16}H_{24}$, b.p. 157–159°/16 mm., is prepared similarly from dicyclopentadiene-quinone (cf. below).

Cyclopentadiene-quinone, $C_{11}H_{10}O_2$, m.p. 78°, a yellowish-green compound, from quinone and one mol. of cyclopentadiene, is enolised by HBr + AcOH into hydroquinone-endomethylene-cyclohexene, which is oxidised by $FeCl_3$ to a yellow *quinone* $C_{11}H_{10}O_2$, m.p. 70° (*Diels,* Ber. **62,** 2350):



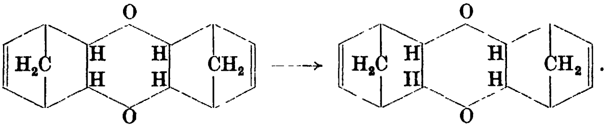
The tetrahydro derivative of the adduct, m.p. 57°, is decomposed by HNO_3 to cyclopentane-1,3-dicarboxylic acid and succinic acid (*Alder,* Ann. **501,** 247). Acetic anhydride brings about dismutation, as shown in the scheme:



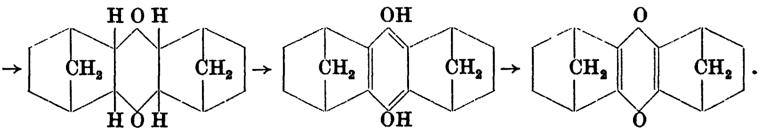
red quinone $C_{16}H_{12}O_2$, m.p. 252°

hydroquinone-diacetate $C_{20}H_{18}O_4$, m.p. 250°.

Dicyclopentadiene-quinone, $C_{16}H_{16}O_2$, m.p. 158°, from quinone and two molecules of cyclopentadiene (*Albrecht,* Ann. **348,** 47; *Diels,* Ann. **460,** 98) is transformed into a *stereoisomer* m.p. 184° by alcoholic KOH (*Alder,* Ann. **501,** 264):



Hydrogenation gives a *tetrahydro* derivative, which is oxidised by bromine to the corresponding *quinol,* m.p. 289°, and with CrO_3 to the *quinone,* m.p. 252°



BICYCLO-[2,2,2]-OCTANES

Just as bicyclo-[1,2,3]-heptanes can be obtained from cyclopentadiene, so representatives of the bicyclo-[2,2,2]-octane series can be prepared from cyclohexadiene and its derivatives by the addition of compounds which contain a conjugated system of double bonds.

The constitution of the resulting compounds is confirmed by the independent synthesis of the parent hydrocarbon and the monoketone by Komppa. This ring system is free from strain as is shown by the heat of combustion of the octanone (*Pirsch*, Ber. **67**, 303).

Bicyclo-[2,2,2]-octane (I), m.p. 169°, which in spite of its melting point is most remarkably volatile, is obtained from the related octanone either via the semicarbazone (*Alder*, *Stein*, Ann. **514**, 27), or from the oxime by reduction to the amine which is converted into the alcohol, m.p. 216–217°, and reduction of the chloride obtained from this (*Komppa*, Ber. **68**, 1267).

Bicyclo-[2,2,2]-octanone-2, *1,4-endoethylene-cyclohexanone-2,* m.p. 176°, *semicarbazone* m.p. 205°, *oxime* m.p. 118°, is formed by heating the Mg salt of hexahydro-homoterephthalic acid (*Komppa*, ib.); it has also been obtained from the following compound. It is oxidised by HNO_3 to cis *hexahydro-terephthalic acid,* m.p. 171° (*Diels*, *Alder*, Ann. **478**, 137).

Bicyclo-[2,2,2]-Δ^5-octenyl-aldehyde-2, *1,4-endoethylene-Δ^5-tetrahydro-benzaldehyde-2* (II), b.p. 84–85°/12 mm., *semicarbazone* m.p. 177°, is obtained from $\Delta^{1,3}$-cyclohexadiene and acrolein in a sealed tube. The *dihydro* compound, m.p. 77°, *semicarbazone* m.p. 192°, can be ozonised via the enol acetate to the bicyclo-octanone (*Diels*, *Alder*, ib.).

Dicarboxylic Acids of the Endo-ethylene Series and Their Anhydrides

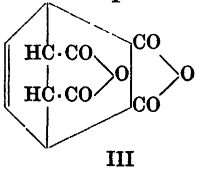
1,4-Endoethylene-Δ^5-tetrahydro-2,3-phthalic anhydride, $C_{10}H_{10}O_3$, m.p. 147°, from $\Delta^{1,3}$-cyclohexadiene and maleic anhydride (*Diels*, Ann. **460**, 98), gives on catalytic hydrogenation with Pd the cis form of *1,4-endoethylene-hexahydro-2,3-phthalic acid,* m.p. 152°, which is converted into the *trans compound* m.p. 243° by hydrochloric acid (*Diels*, Ann. **478**, 142). The constitution is deduced from its oxidation to hexahydro-mellophanic acid (id. Ber. **62**, 2087).

1,4-Endoethylene-Δ^2-tetrahydro-2,3-phthalic anhydride, m.p. 158°, isomeric with the previous compound, has been prepared from the corresponding dibromomaleic anhydride adduct, m.p. 252°, by hydrogenating the double bond and removing bromine, and also by reduction of the reactive double bond and loss of water, from

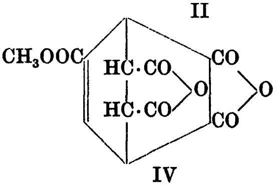
1,4-Endoethylene-$\Delta^{2,5}$-dihydro-2,3-phthalic acid, a condensation product of cyclohexadiene and acetylene-dicarboxylic acid (*Diels*, Ann. **490**, 236).

More complex anhydrides have successfully been obtained by condensing *maleic anhydride with coumalin* or its derivatives, either in boiling xylene or in the molten mixture (*Diels*, Ann. **490**, 257). From coumalin, methyl coumalate, dimethyl-coumalin, and isodehydracetic acid the following compounds were prepared: (I) $C_{12}H_8O_6$, m.p. 349°, tetramethyl ester, m.p. 131°; (II) $C_{14}H_{10}O_8$, m.p. 331°, pentamethyl ester, m.p. 138°; (III) $C_{14}H_{12}O_6$, m.p. 274°, tetramethyl ester, m.p. 155°; and an acid corresponding to the anhydride (IV) $C_{15}H_{16}O_{10}$, m.p. 325°, pentamethyl ester, m.p. 204°.

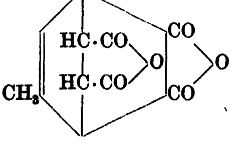
I



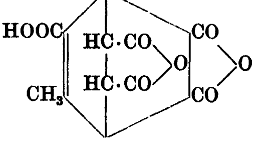
II



III

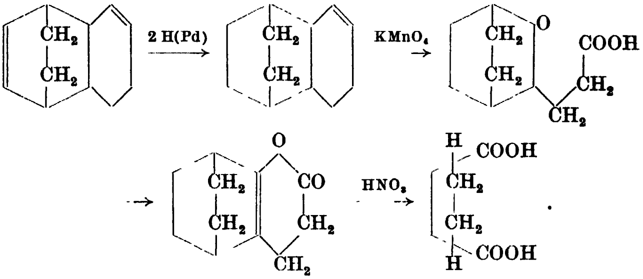


IV

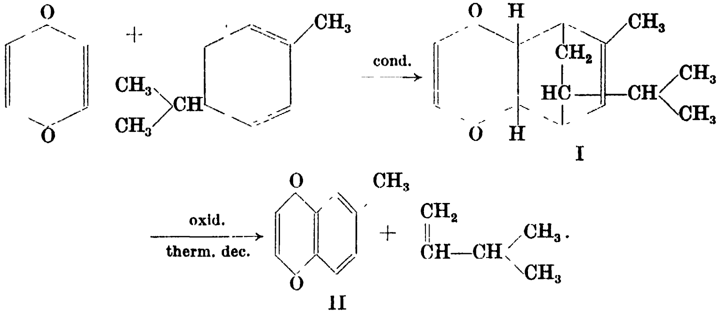


1,4-Endoethylene-decalins and -Tetradecahydro-anthracenes

Dicyclohexadiene, $C_{12}H_{16}$, the analogue of dicyclopentadiene, is a liquid hydrocarbon formed by dimerisation of $\Delta^{1,3}$-cyclohexadiene. Selective reduction of this compound gives the *dihydro compound* $C_{12}H_{18}$ b.p. 107–108°/16 mm. By oxidising this product *Alder* has succeeded in opening the rings step by step, obtaining first the oily *keto-acid* $C_{11}H_{16}O_3$ (methyl-ester-oxime m.p. 86°) through the *enol-lactone* m.p. 69° and finally *cis hexahydro-terephthalic acid* m.p. 171° (*Alder*, Ann. **496**, 197).



The *quinone addition products* of the *cyclohexadienes* are structural and stereochemical analogues of the cyclopentadiene derivatives and can be oxidised in the same way to the corresponding quinones ("aromatisation"), after enolisation. It should be noticed that on thermal decomposition the ethylene bridge is lost as a whole, which throws light on the structure of the cyclohexadiene derivative, e.g.:

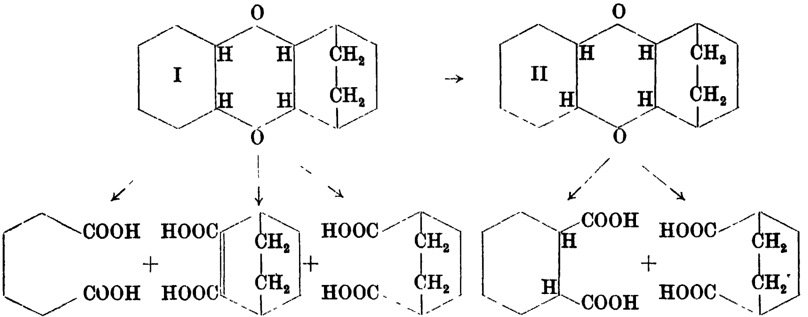


Cylcohexadiene-quinone, $C_{12}H_{12}O_2$, m.p. 98°, from quinone and one mol of cyclohexadiene (*Diels*, Ber. **62**, 2347), can be reduced to a cis *tetrahydro compound* m.p. 65°, which, on oxidation with HNO_3, gives cis *hexahydro-terephthalic acid* m.p. 171° (*Alder*, Ann. **501**, 253).

Quinone-α-phellandrene condensation product $C_{16}H_{20}O_2$ (I, above), m.p. 119°, see *Diels*, Ber. **62**, 2347.

Dicyclohexadiene-quinone, $C_{18}H_{20}O_2$, m.p. 197°, is the product of the action of two mols of cyclohexadiene on one mol of quinone. It melts at 197°, then undergoes isomeric change and melts at 268° (*Diels*, Ber. **62**, 2337; *Alder*, Ann. **501**, 288).

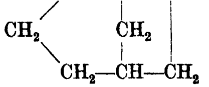
Butadiene-quinone-cyclohexadiene adduct, $C_{16}H_{18}O_2$, m.p. 137°, is obtained from monobutadiene-quinone and $\Delta^{1,3}$-cyclohexadiene. Its *tetrahydro compound* (I), m.p. 157°, undergoes isomeric change in presence of Ac_2O to (II), m.p. 184°, as is proved by degradation with HNO_3 (id. ib.):



Adipic acid 1,4-Endoethylene-Δ^2-tetrahydro-2,3-phthalic acid cis-Hexahydro-terephthalic acid trans-Hexahydro-phthalic acid m.p. 217° cis-Hexahydro-terephthalic acid m.p. 171°.

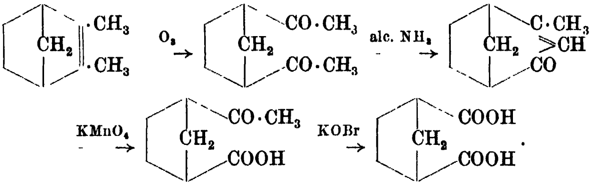
BICYCLO-[1,2,3]-OCTANES

Bicyclo-[1,2,3]-octanone-2, *keto-bicyclo-[1,2,3]-octane*



which is a representative of this bicyclic system, has been obtained by distilling the calcium salt of 1-carboxy-cyclohexane-2-acetic acid (*Komppa*, Ber. **36**, 3610).

5-Methyl-Δ^5-bicyclo-[1,2,3]-octenone-7, $C_9H_{12}O$, b.p. 100–105°/9 mm. is a condensation product of santene diketone, $C_9H_{14}O_2$, obtained by treating santene (pp. 185, 270) with ozone or with $KMnO_4$, santene glycol being an intermediate product. NaOEt or, preferably, alcoholic NH_3 are used as condensing agents (*Semmler*, Ber. **40**, 4844). Its constitution is clear from the fact that it is oxidised first to a methyl-keto-acid $C_8H_{12}O_3$ and then to cis cyclopentane-1,3-dicarboxylic acid (id. Ber. **41**, 866).



Other compounds which are more fully described in the chapter on Terpenes, viz. *endocamphene* (p. 269), cyclic *homocamphenilone* (p. 269), *homocamphor* (p. 321) and *homo-epicamphor* (p. 321), also belong to this system.

BICYCLO-[1,3,3]-NONANES

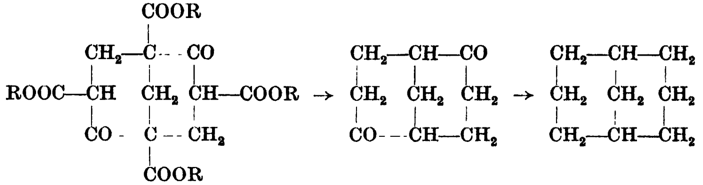
Two 6-rings, linked together in 1,3-position, form a bicyclic system which consists of an eight-membered ring with a methylene bridge in the p-position. It occurs in the compounds:

Bicyclo-[1,3,3]-nonane-2,6-dione-1,3,5,7-tetracarboxylic methyl ester (I), m.p. 163–164°, a condensation product of methylene-mono- and -di-malonic esters with NaOEt. Decomposition of this ester with HCl yields the ketone

Bicyclononanedione (II), $C_9H_{12}O_2$, m.p. 141°. The *disemicarbazone* of (II), m.p. 226°, when heated with NaOEt, gives the hydrocarbon:

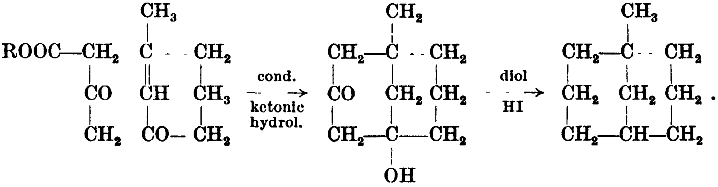
Bicyclononane (III), C_9H_{16}, m.p. 145–146°, b.p. 168·5–170°, which is a completely strainless arrangement (*Meerwein*, Ann. **398**, 223; *Rabe*, J. pr. Ch. **104**, 161).

I II III



A second method of synthesising this ring system is due to *Rabe*, who condensed cyclohexenones with ethyl acetoacetate.

1-Methyl-bicyclo-[1,3,3]-nonane, $C_{10}H_{18}$, b.p. 176–178°, a liquid with a terpene-like odour, is obtained from 1-methyl-Δ^1-cyclohexenone-3 and acetoacetic ester by the steps shown (Ber. **37**, 1671)



9-Methyl-3-isopropyl-bicyclo-[1,3,3]-nonane, $C_{13}H_{24}$, b.p. 232–233° is prepared in the same way from ethyl acetoacetate and carvone (id., Ber. **36**, 225; **37**, 1667).

III. TERPENES AND RESINS[1]

BY MARIA LIPP, née BREDT-SAVELSBERG

The *volatile* or *essential oils* are obtained from many plants, chiefly *Coniferae* and species of *Citrus*, usually by distillation with steam, and less frequently by pressing or by extraction with volatile solvents or fats. They contain, together with various other compounds, certain hydrocarbons of the formula $C_{10}H_{16}$, which are called **terpenes**.

The terpenes are an important, and often the principal, constituent of many essential oils which are of importance in the perfumery industry. The accurate recognition of individual terpenes and the possibility of separating them from one another are chiefly due to the painstaking researches of *Otto Wallach*, who has brought order and system out of this chaotic mass of hydrocarbons (see *Ruzicka*, J. **1932**, 1582).

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[1] *Wallach*, *Terpene und Campher* (2nd ed.), Leipzig 1914; *Gildemeister*, *The Volatile Oils* (2nd ed.), London 1922; (3rd [German] ed., Miltitz-Leipzig 1928–1931); *Simonsen*, *The Terpenes*, Cambridge University Press 1931.

The natural terpenes have been found to include open-chain, monocyclic and bicyclic compounds, and thus to belong to very different classes of substances.

The reasons why they are all treated here in one section are not only their common origin in plants and the historical development of terpene investigation, but also the fact that the various chemical classes are closely related to one another, both by various chemical interconversions and, in all probability, also biologically. Olefinic terpenes and their various derivatives can be converted into cyclic terpenes by ring closure, e.g. dihydro-myrcene into cyclo-dihydromyrcene, and linalool into dipentene; conversely cyclic terpenes by ring fission give olefinic terpenes; e.g. isopulegol gives citronellal. Further, bicyclic terpenes and their derivatives can be converted into monocyclic terpenes and their derivatives, e.g. carene into sylvestrene, pinene into dipentene, camphor into carvenone. On the other hand, monocyclic terpenes are not usually transformed with ease into bicyclic terpenes, and the conversion of dihydrocarvone hydrobromide into carone by means of alcoholic potash is one of the few exceptions.

Isoprene C_5H_8 and the terpenes $C_{10}H_{16}$ are identical in composition, a fact of more than schematic significance. This was clearly recognised by *Wallach*, who suggested the name *hemiterpene* for isoprene. Indeed, isoprene is both obtained as a decomposition of the terpenes $C_{10}H_{16}$ and is reconverted by dimerisation into compounds of the formula $C_{10}H_{16}$ (*Wallach*, Ber. **24**, 1525). According to the conditions, the dimerisation may result in open-chain molecules, the **acyclic or olefinic terpenes**, or in closed ring molecules, the **monocyclic terpenes** (*Wagner-Jauregg*, Ann. **496**, 52). When the two isoprene residues combine to form a chain, an eight-membered carbon chain with methyl or methylene groups attached to the 2- and 6-positions is by far the chief product; on ring closure two different kinds of six-rings are formed, one carrying a methyl and an isopropyl group—or the corresponding unsaturated groups, methylene, isopropylidene and isopropenyl—in 1- and 4-positions with respect to one another, and the other carrying the same groups in the 1,3-positions. They are called *dipentene* and *diprene* respectively (*Aschan*, Ann. **461**, 12). The first type is closely related to p-cymene, p-methyl-isopropylbenzene (vol. III), and the second to m-cymene, m-methyl-isopropylbenzene, and they are the partially reduced derivatives of these aromatic hydrocarbons. Limonene, dipentene, terpinolene, terpinene and phellandrene are dihydro-p-cymenes, while sylvestrene and carvestrene belong to the meta series. The combination of two isoprene residues to produce dipentene or diprene is a special case of the **diene synthesis** (p. 86).

The **bicyclic terpenes** are, in theory, derived from dipentene by a further ring closure, either by the formation of a new C — C bond between two ring atoms in the 1,3-position (*sabinane* group), or by the central C-atom of the isopropylidene group linking itself to two atoms of the 6-ring, either in the 1,2-position in the case of the *carane* group which can also be derived from diprene, in the 1,3-position in the case of the *pinane* group, or in the 1,4-position in that of the *camphane* group. In practice, such syntheses have succeeded only in the carane and sabinane groups. Derivatives of the former group had been synthesised before any of its members had been detected in nature. The other ring systems have been synthesised, if at all, by more laborious methods, as for example those used in the synthesis of camphor and fenchone. Though bicyclic terpenes have been built up from monocyclic ones only in a few cases, the opposite process, the conversion of bicyclic into monocyclic terpenes, is very easily achieved in all the four groups. This justifies the common treatment of substances which at first sight, seem to differ so widely in their structure.

The terpenes can thus be divided into the following groups: *acyclic terpenes* with three double bonds, which can add on six monovalent atoms or groups, *monocyclic terpenes* with two double bonds, which can add on four monovalent atoms or groups, and *bicyclic terpenes* which have only one double bond and cannot add on more than two monovalent atoms or groups, if the carbon skeleton is to remain intact. Finally, completely saturated *tricyclic terpenes* (tricyclene, cyclofenchene) have been obtained synthetically, but no such compounds have yet been detected in essential oils.

The polymerisation of isoprene is not necessarily complete when two molecules have united, but, in theory, compounds such as $C_{15}H_{24}$ (from three molecules), $C_{20}H_{32}$ (from four molecules), and $(C_5H_8)_x$ (from x molecules) are conceivable. In fact, higher boiling hydrocarbons corresponding to these formulae have been isolated from many essential oils, gums, and balsams. The compounds $C_{15}H_{24}$ are called **sesquiterpenes**, those of the formula $C_{20}H_{32}$ **diterpenes**, and those of the formula $(C_5H_8)_x$ **polyterpenes**. In a few cases it has been found possible to cause isoprene to combine with terpenes, as in the case of cyclo-isoprene-myrcene (cf. *Wagner-Jauregg*, Ann. **496**, 52). The hypothesis that sesquiterpenes, diterpenes etc. are built up from isoprene molecules according to some common principle shows itself to be of great value in the determination of the constitution of these substances. It was first applied as a working hypothesis, but may now be said to have a firm experimental basis in the transformations and decompositions which have been observed (p. 322). It has been found to be of great use not only for the terpenes, polyterpenes and rubber, but also in the study of resin acids and some of the natural dyes (*Ruzicka*) (see bixin, lycopin, carotene etc. in the section "Natural Colouring Substances" (p. 407).

In *preparing* and *isolating pure terpenes* the same difficulties are met as have been described in the case of the dihydrobenzenes. In almost every case a mixture of isomeric hydrocarbons is obtained, which are very similar to each other, and the extraction from such a mixture of a completely homogeneous terpene is very troublesome. For this reason the difficulties of elucidating their structure have been great, but thanks to the work of *Aschan*, *Baeyer*, *Bredt*, *Komppa*, *Perkin jr.*, *Semmler*, *Wagner*, and others, and above all, of *Wallach*, the constitution of most of the terpenes and their interrelationships are to-day firmly established. In many cases, such as those of dipentene, terpinene, sylvestrene, carvestrene, camphene, and fenchene, a complete synthesis has been carried out; in other, as with pinene and phellandrene, a partial synthesis has been effected.

Various alcohols, aldehydes, and ketones are derived from the terpenes. Their general formulae are $C_{10}H_{14}O$, $C_{10}H_{16}O$, $C_{10}H_{18}O$

and $C_{10}H_{20}O$, and some of them occur in essential oils together with terpenes and often separate out as solids, as with Japan camphor. They were formerly classified as *camphors*, although they belong to several different classes of substances, just as the terpenes themselves do; they are olefinic, monocyclic and bicyclic. At present the constitution of most of them is known and the collective designation as "camphors" is of merely historical interest. Thus as well as the terpenes and their addition products, this section includes the *terpene alcohols*, the *terpene aldehydes*, and the *terpene ketones* and compounds derived from them.

Terpene alcohols, aldehydes and ketones are more easily isolated and purified than the terpenes themselves, since many of them crystallise very well, and others are readily recovered as pure substances from characteristic derivatives which they form. Many of these compounds, e.g. camphor, fenchone, menthone, α-terpineol and others, have been successfully synthesised, once their constitution had been elucidated. Synthesis has gone a stage further—the same is true, to a degree, of terpenes—in producing new compounds not yet detected in essential oils, but resembling the natural products in constitution and behaviour to such an extent that they may be regarded as artificial terpene alcohols and ketones.

The oxygenated derivatives of the sesquiterpenes, the diterpenes and the polyterpenes, mainly alcohols and ketones, are discussed in connection with the hydrocarbons to which they are related. The investigation of their constitution has made rapid progress as a result of the insight which has been obtained into the structure of the corresponding hydrocarbons. Attempts to synthesise compounds of this group have only been made during the last ten years, but have already been successful in certain cases (see e.g. nerolidol).

Physical properties.—The pure terpenes $C_{10}H_{16}$ are colourless liquids of high refractive power, though a few, like camphene, are solids at ordinary temperature. They boil without decomposition between 150–180°, are easily volatile in steam and possess a characteristic and usually pleasant odour. Most terpenes are optically active and of some antimeric forms are known, while dipentene and carvestrene are examples of racemic terpenes.

Chemical behaviour.—(1) The terpenes *polymerise* readily.

(2) Under the influence of acids many terpenes change very easily into *isomers* which differ in the arrangement of the bonds. Thus α-terpinene becomes γ-terpinene by a simple shift of the double bond, myrcene → cyclodihydromyrcene by ring closure, pinene → dipentene by change of ring system.

(3) Some terpenes are easily *oxidised* even by the oxygen of the air, e.g. α-pinene and β-phellandrene, and often with resinification (*Kingzett*, J. **1894**, 51). The formation of benzene derivatives in the oxidation of terpenes is significant. α-Pinene, e.g., is converted by iodine into p-cymene, and by nitric acid into p-toluic and terephthalic acids, etc.

(4) The importance of *addition reactions* has already been pointed out in connection with the classification of terpenes:

(a) The terpenes on reduction take up *hydrogen* and give hydroterpenes (*Semmler*, Ber. **36**, 1033).

(b) The addition of *chlorine, bromine* or *hydrogen halides*, in cold AcOH, gives *halogen substitution products* of the *hydroterpenes*. Many of these crystallise well and are useful in characterising and distinguishing the terpenes. They are reconverted into terpenes by heating with NaOAc in AcOH, or with bases such as aniline (*Semmler*, Ber. **34**, 708). These halogen compounds are the intermediates in the conversion of terpenes into terpene alcohols. Some of them can be obtained from terpene alcohols.

(c) *Nitrosyl chloride* NOCl (*Tilden*), or an alkyl nitrite, glacial acetic acid and hydrochloric acid, react with most terpenes to give well defined *terpene nitrosochlorides.* These compounds are often unstable, but react with primary and secondary bases to form stable *terpene nitrolamines,* or, by loss of HCl, *nitroso-terpenes,* which are useful for characterisation. By means of the latter compounds terpenes can be converted into terpene ketones (see limonene nitrosochloride).

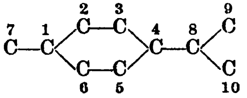
(d) Certain terpenes unite with N_2O_4, forming *nitrosates* $C_{10}H_{16}(NO_2)_2$, and with N_2O_3, yielding *pseudo-nitrosites* (nitrites) $C_{10}H_{16}(NO)NO_2$ (*Wieland,* Ann. **424,** 71). The nitrosochlorides, nitrosates and pseudonitrosites are bimolecular in the solid state and should therefore be regarded as *bis-nitrosochlorides, bis-nitrosates* and *bis-pseudonitrosites.* In their reactions they behave as monomolecular compounds (*Baeyer,* Ber. **28,** 648; **29,** 10).

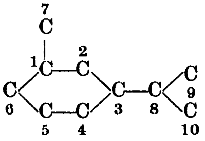
(e) The terpenes are converted by *ozone* into *ozonides,* and with dilute $KMnO_4$ solution they give *glycols* by the addition of 2 OH. Both reactions are important for determining their constitution. For their reaction with perbenzoic acid see *Meerwein,* J. pr. **113,** 9, and for the addition of trichloroacetic acid and of formaldehyde see *Reychler,* Ber. **29,** 695 and *Kriewitz,* Ber. **32,** 57.

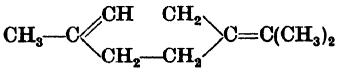
Nomenclature.—In most cases the terpenes are described by names derived from the plants in the essential oils from which they were first observed, or are most abundantly found. Since many terpenes, formerly considered homogeneous, were later found to be mixtures, the terpenes isolated from them have been distinguished from each other by prefixing Greek latters, e.g. α-, β-, and γ-terpinene, α- and β-pinene. On the other hand, certain terpenes, e.g. limonene, which were found in several different essential oils, were believed to be different and were called by several names.

Baeyer, in accordance with the Geneva nomenclature, suggested that the cyclic terpenes containing the same carbon skeleton as p-cymene, the dihydro-p-cymenes, should be called *terpadienes*; the tetrahydro-cymenes would then be *terpenes,* and hexahydro-cymene *terpane. Wagner,* on the other hand, called hexahydro-cymene *menthane,* tetrahydro-cymenes *menthenes,* and the dihydro-cymenes or terpenes *menthadienes* (Ber. **27,** 1636, footnote). This latter system, with the help of the prefixes o-, m- and p-, has been generally accepted.

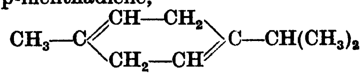
Rational names for the dihydrocymenes and their derivatives can be obtained by allotting numbers to the carbon atoms:



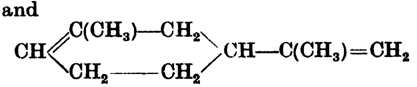


Hence, dihydro-p-cymene of formula 

is described as $\Delta^{1,4(8)}$-p-menthadiene,

the dihydro-p-cymene 

as $\Delta^{1,4}$-p-menthadiene and

the dihydro-m-cymene 

as $\Delta^{6,8(9)}$-m-menthadiene.

For the nomenclature of the bicyclic terpenes see p. 239.

The terpenes will be discussed in the following groups:—

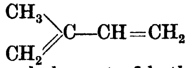
A. Olefinic terpene or terpenogen group.
B. Monocyclic terpene or menthane group.
C. Bicyclic terpene groups:
  I. Sabinane or tanacetane group:
  II. Carane group.
  III. Pinane group.
  IV. Camphane group.
D. Sesquiterpene and polyterpene groups.

To the hydrocarbons of each group must be added the alcohols, aldehydes and ketones, and their transformation and degradation products.

A. OLEFINIC TERPENE OR TERPENOGEN GROUP

This group comprises a number of ethylenic hydrocarbons, alcohols, aldehydes and acids with open carbon chains. They occur in essential oils, or are the products of the reactions of compounds found in these oils. They are distinguished by the fact that, as a rule, they are easily converted into hydroaromatic and aromatic substances. Before dealing with them, reference must be made to

Isoprene, *β-methyl-butadiene* (I, 116),



$$\begin{matrix} CH_3 \\ CH_2 \end{matrix}\!\!>\!C\text{—}CH{=}CH_2$$

which has already been mentioned as the structural element of both olefinic and cyclic terpenes (*Waterman,* Rec. **48**, 1084, 1191; J. Franklin Inst. **221**, 436; *Wagner-Jauregg,* Ann. **488**, 176; **496**, 52; cf. caoutchouc p. 338). Pure isoprene has the following physical constants: b.p. 34·076°/760 mm., m.p. about —146°, d_4^{20} 0·6805, n_D^{20} 1·42160 (*Vassiljev,* C. 1936 II 1884).

(1) Olefinic Terpenes

Myrcene, $C_{10}H_{16}$, $Me_2C{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}C({:}CH_2){\cdot}CH{:}CH_2$, b.p. 67°/20 mm., d^{15} 0·8025, n_D 1,4673, occurs in bay berry oil together with *l*-phellandrene and unsaturated aromatic phenols, in the essential oils of *Lippia citriodora* and *Barosma venusta* (*Goulding,* J. **105**, 2613), and in hop oil (*Semmler,* Ber. **44**, 2009; *Rabak,* J. Agr. Res. Washington **2**, 115). Artificially it is made from linalool (p. 202) by dehydration with $KHSO_4$ or with iodine (*Brooks,* Am. **40**, 845) or by catalytic dehydration (cf. *Ono,* Bull. Japan **2**, 16). It adds four atoms of bromine and is reduced by Na + EtOH to **β-dihydromyrcene** $C_{10}H_{18}$, b.p. 167–169°/770 mm., *tetrabromide* m.p. 88°. The latter is also obtained from linalool (*Longinov,* Bull. **51** (1932), 636) and undergoes isomeric change in the presence of AcOH + H_2SO_4 to *cyclo-dihydromyrcene* (*Semmler,* Ber. **34**, 3126). The complete hydrogenation of myrcene, which can only be done by catalytic methods, yields 2,6-dimethyl-octane, while ozonisation gives succinic acid (*Ruzicka, Stoll,* Helv. **7**, 271). When heated to 250–260°, under pressure, myrcene polymerises to α-camphorene (p. 336) and polymyrcenes which cannot be distilled. For cyclo-isoprene-myrcene see p. 325.

Ocimene, $C_{10}H_{16}$, $CH_2{:}CMe{\cdot}CH_2{\cdot}CH_2{\cdot}CH{:}CMe{\cdot}CH{:}CH_2$ (*Enklaar,* Rec. **45**, 337), b.p. 81°/30 mm., d^{15} 0·8031, can be extracted from the essential oil of *Ocimum basilicum,* from flowering *Tagetes glandulifera* and from the fruit of *Evodia rutaecarpa* (*Asahina,* Acta physicochim. **1** (1922), 67). It differs from myrcene in the position of two double bonds. When reduced with Na + EtOH it takes up two H-atoms and gives *dihydro-ocimene* b.p. 68–70°/23 mm. On ozonisation, acetone, methyl-glyoxal and malonic dialdehyde are formed (*Enklaar,* Rec. **27**, 422). For the oxidation with $KMnO_4$ see id. ib. **45**, 337; Chem. Weekbl. **21**, 101. If ocimene is distilled at ordinary pressure, it undergoes a rearrangement into the less volatile **allo-ocimene** $Me_2C{:}CH{\cdot}CH{:}CH{\cdot}C(Me)'{:}CH{\cdot}Me$, b.p. 95°/29 mm., d^{18} 0·8132 (id. Rec. **36**, 215; Chem. Weekbl. **23**, 175). See p. 252 for allo-ocimene from pinene and for diene syntheses with allo-ocimene.

Anhydro-geraniol, $C_{10}H_{16}$, b.p. 172–176°, from geraniol with potassium bisulphate at 170°, takes up 6 atoms of bromine (*Semmler*, Ber. **24**, 682) and is a mixture of the limonene and the terpinolene forms[1], like geraniol (see below) (*Grignard*, Bull. **45** (1929), 809). **β-Linaloolene,** $C_{10}H_{18}$, b.p .161–162°, d_4^{20} 0·7601, n_D^{20} 1·4362, has been obtained from rhodinol-glycol (*Longinov*, Bull. **51** (1932), 636).

(2) Olefinic Terpene Alcohols

d-Citronellol, $C_{10}H_{20}O$, b.p. 110·5–111°/10 mm., $[\alpha]_D^{20}+4{\cdot}14°$, a mixture of $CH_2{:}CMe{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CHMe{\cdot}CH_2{\cdot}CH_2OH$ (*limonene form*) and $Me_2C{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CHMe{\cdot}CH_2{\cdot}CH_2OH$ (*terpinolene form*) (but cf. *Naves*, C. r. **200**, 1112), was first obtained by reducing d-citronellal (*Rupe*, Helv. **7**, 541), into which it is reconverted by oxidation. It occurs in many essential oils and is the main constituent of Java citronella oil. The *l*-form is found, together with geraniol, in various oils from roses, geranium and pelargonium. It is a colourless oil with a pleasant smell of roses. For the relation between structure and odour cf. *v. Braun* and *Gossel*, Ber. **57**, 373. For its detection as the *Ag-salt of the acid phthalate*, m.p. 126°, see *Penfold*, J. Royal Soc. New South Wales **68**, 80. It has been shown to be 2,6-dimethyl-octene-(1- and 2-)ol-8 by oxidising it with ozone (*Harries*, Ber. **41**, 2191; *Grignard*, Bull. **37** (1925), 546; **45** (1929), 809; *Helferich*, Ber. **64**, 104), and with $KMnO_4$ (*Kötz*, J. pr. **107**, 193). The question of the constitution of citronellol has been complicated by the existence of a supposed isomer, **rhodinol,** b.p. 113–115°/14 mm., which on ozonisation gives the same products as citronellol and thus also seems to be a mixture of the 2,6-dimethyl-octene-1 and -2-ols, a conclusion supported by the Raman spectra (*Naves*, C. r. **200**, 1112), the rotatory dispersion (*Angla*, C. r. **198**, 2241) and careful study of the ozonisation products (*Doeuvre*, C. 1935 I 1310). Samples of citronellol and rhodinol sometimes seem to differ in the relative proportions of the limonene and terpinolene forms. *d*-Rhodinol has an intense rose odour and is obtained by treating *d*-citronellyl acetate with HBr, heating with sodium acetate at 160° and finally hydrolysing. Its rotation is the same as that of the *d*-citronellol which serves as starting material, but the chemical properties are different; for instance, it is oxidised to rhodinal (p. 204) by CrO_3 (*Barbier*, C. r. **157**, 1114; *Grédy*, C. r. **195**, 313). For its preparation from citronellyl benzoate see *Doeuvre*, Bull. **45** (1929), 1098, and for hydroxy-citronellol see *Sornet*, Rev. Ch. Ind. **38** (1929), 34.

Geraniol, $C_{10}H_{18}O$, b.p. 122–125°/20 mm., is a mixture of $CH_2{:}CMe{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CMe{:}CH{\cdot}CH_2OH$ and $Me_2C{:}CH{\cdot}CH_2\ CH_2{\cdot}CMe{:}CH{\cdot}CH_2OH$ (*Escourrou*, Bull. **43** (1928), 1088, 1101; *Blumann*, Ber. **44**, 2591; *Kotz*, J. pr. **107**, 193). It is the chief alcoholic constituent of the oils of roses, geranium, pelargonium, and of lemongrass oil and palmarosa oil (from *Cymbopogon Martini*, Stapf, var. *motia*) etc. Its esters are found in many essential oils; it is, indeed, the most widely distributed aliphatic terpene alcohol. It forms a characteristic crystalline compound with calcium chloride by means of which it can be separated from the other constituents of essential oils. *Diphenyl-carbamic ester* m.p. 82°; *tetrabromide* m.p. 70° (*Elze*, C. 1929 I 2249). Geraniol is optically inactive and is related to citral in the same way as citronellol to citronellal. The synthesis of citral is equivalent to that of geraniol. Geranyl chloride has been used for synthesising farnesol and nerolidol (*Ruzicka*, Helv. **6**, 492). Cold mineral acids convert geraniol into a stereoisomeric alcohol,

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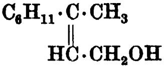
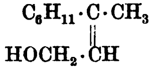
[1] These terms are used to indicate that the three terminal C-atoms form either an isopropenyl group, as in limonene (p. 208), or an isopropylidene group, as in terpinolene (p. 209).

Nerol, b.p. 225°, d^{15} 0·880, which is thought to be the cis form, while the trans configuration has been attributed to geraniol (*Lab. Dauphin*, Parf. **2**, (1927), 40)



$$\begin{array}{l} C_6H_{11}\cdot \overset{}{C}\cdot CH_3 \\ \;\;\;\; \| \\ HC\cdot CH_2OH \end{array}$$

Geraniol



$$\begin{array}{r} C_6H_{11}\cdot C\cdot CH_3 \\ \| \;\;\;\;\;\;\;\;\; \\ HOCH_2\cdot CH \;\;\;\; \end{array}$$

Nerol

Nerol occurs abundantly in the oil of *Helichrysum angustifolium,* and also in the extract oils of neroli, petitgrain, bergamot, cyclamen (*Elze*, C. 1928 II 499) and in linaloe oil, partly in the free state and partly esterified. Nerol is very similar to geraniol, but does not form a solid calcium chloride compound. It gives a *tetrabromide* m.p. 119° and a *diphenyl-urethane* m.p. 52° (*Elze*, l. c.). It differs from geraniol also in its greater tendency to ring closure and dehydrogenation, and in its smell. Pure neryl acetate has the odour of orange flowers, while that of geranyl acetate is fruity. On oxidation first with $KMnO_4$ and then with CrO_3, acetone and laevulic acid are formed, and in the same quantities as in the oxidation of geraniol (*Blumann*, Ber. **44**, 2593). Geraniol and nerol are related to one another in the same way as citral *a* and citral *b*, geraniol corresponding to citral *a* and nerol to citral *b*. For the esters of nerol, see *Reclaire*, C. 1929 I 2249.

Linalool, $C_{10}H_{18}O$, b.p. 197–199°, d^{20} 0·8702, is regarded as a mixture of $CH_2 : CMe \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CMe(OH) \cdot CH : CH_2$ and $Me_2C : CH \cdot CH_2 \cdot CH_2 \cdot CMe(OH) \cdot CH : CH_2$, because of its close relationship to geraniol and citral. Its *l*-form (*licareol*) occurs in linaloe oil from *Ocotea caudata*, Meg. (*licari kanali*), in lavender oil, bergamot oil, oil of limes ($[\alpha]_D$—20° 7′)[1], origanum oil, etc., while *d*-linalool (*coriandrol*) is found in coriander oil and the oil of oranges ($[\alpha]_D$ + 19°18′) and of orange blossom. *Phenylurethane* m.p. 65—66°; *α-naphthylurethane* m.p. 53°. *d, l*-Linalool has been prepared from geranyl chloride with aqueous K_2CO_3, and by reducing dehydrolinalool (see below) (*Dupont*, C. 1914 II 932; *Ruzicka*, Helv. **2**, 182). The odour of linalool resembles that of lilies of the valley. When it is oxidised with chromic acid, rearrangement into geraniol takes place, and citral is produced. For the formation of α-camphorene and cyclo-isoprene-myrcene, and dehydration to dipentene, see *Semmler*, Ber. **47**, 2079; *Vinogradova*, Ber. **64**, 1991.

Citronellol, geraniol, and linalool are reduced with H_2 on Ni, Pt or Pd first to the corresponding 2,6-dimethyl-octanols: further reduction of all of them gives the same 2,6-dimethyl-octane $C_{10}H_{22}$ which is also obtained from ocimene (see above). This shows that all these compounds have the same carbon skeleton (*Enklaar*, Ber. **41**, 2084).

Dilute sulphuric acid converts linalool easily, and geraniol less easily, into inactive *terpin hydrate* (p. 219) (*Tiemann*, Ber. **28**, 2137): in the same way with formic acid or a mixture of sulphuric and acetic acids geraniol is converted with some difficulty into solid α-terpineol, m.p. 35°, and linalool comparatively easily. In the course of these reactions linalool partly rearranges to geraniol, while conversely geraniol can be transformed into *d, l*-linalool (*Stephan*, J. pr. **60**, 244; *Ono*, Bull. Japan **2**, 16; *Horiuchi*, J. Japan **36**, 191). By a more vigorous action of the same reagents terpenes such as terpinolene (p. 209), dipentene (p. 208), and terpinene (p. 210) are formed, together with terpin hydrate and terpineol. Similar products have been obtained by heating linalool with anhydrous oxalic acid (*Mochida*, Pharm. Japan **54** (1934), 133).

In these ring closures the C-atoms 3 and 8 of the 2,6-dimethyl-octadiene chain are linked together, in the same way as in the formation of isopulegol from citronellal (see below). Ring closure is also possible between the atoms 2 and 7 with the formation of exocyclic alcohols of trimethylcyclohexene, α- **and β-cyclogeraniol,** the alcohols corresponding to α- and β-cyclocitral. These compounds are obtained by treating esters of geraniol with concentrated acids, and especially with phosphoric acid (Germ.Pat. 138,141).

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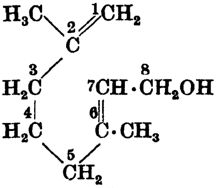
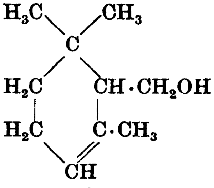
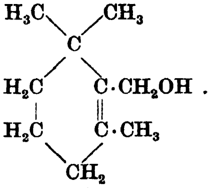
[1] The rotatory power of all these alcohols varies, and depends on the source and the method of extraction; this may be due to a difference in proportions in a mixture, or to racemisation.


Geraniol (*limonene form*)


I


II

α-Cyclogeraniol, $C_{10}H_{18}O$ (I), b.p. 213–217°, b.p. 97–98°/12 mm., *phenylurethane* m.p. 75°, can be obtained not only by this ring closure of geraniol esters, but also in an almost pure state by reducing the ethyl ester or the amide of α-cyclogeranic acid with Na + EtOH (*Bouveault,* Bull. 7 (1910), 354), and by the action of Al isopropoxide on cyclocitral (*Kuhn,* Ber. **69,** 1555).

β-Cyclogeraniol, $C_{10}H_{18}O$ (II), m.p. 43–44°, b.p. 101–102°/11 mm., is the chief product of the reduction of a mixture of α- and β-cyclocitral (p. 205) with aluminium isopropoxide and isopropyl alcohol, and can be separated from α-cyclogeraniol owing to the ease with which it crystallises. It has a pleasant smell like that of eucalyptus, which differs from the somewhat flowery odour of the α-form (*Kuhn,* Ber. **67,** 357).

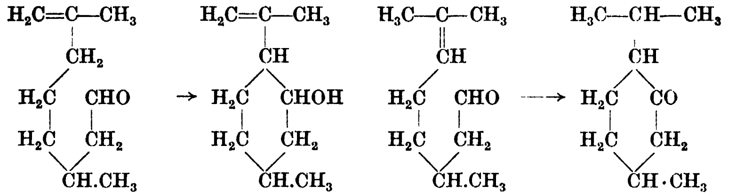
As has already been mentioned, the constitution of the olefinic terpene alcohols, aldehydes and acids discussed below has been deduced from their oxidation products. One of these, *methyl-heptenone,* described in vol. I, 276, has played an important part in this connection. The natural product as well as the synthetical product prepared from citral consists of about 80% $Me_2C{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CO{\cdot}Me$ and 20% $CH_2{:}C(Me){\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CO{\cdot}Me$ (*Grignard,* C. r. **176,** 1860; **177,** 669; *Escourrou,* Bull. **39** (1926), 1121). This is evidence for the constitutional formulae of citronellol, geraniol and linalool given above. On the other hand, methyl-heptenone has been used for the synthesis of several compounds belonging to this group, such as *d, l*-rhodinol (Germ.Pat. 423,544) and dehydro-linalool (*Rupe,* Helv. **12,** 1133). With zinc and allyl iodide it condenses to **homo-linalool** $C_6H_{11}{\cdot}C(Me)(OH){\cdot}CH_2{\cdot}CH{:}CH_2$, b.p. 102–104°/14 mm. (*Tiemann,* Ber. **29,** 693; *Léser,* C. r. **127,** 763; *Escourrou,* Bull. **39** (1926), 1249). α-Alkyl-geraniols are obtained from citral and alkyl-magnesium compounds (Germ.Pat. 153,120; *Ruzicka,* Helv. **18,** 439).

(3) Olefinic Terpene Aldehydes

Citronellal (I), $C_{10}H_{18}O$, a mixture of much $CH_2{:}C(CH_3){\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CH(CH_3){\cdot}CH_2{\cdot}CHO$ and a little $(CH_3)_2C{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CH(CH_3){\cdot}CH_2{\cdot}CHO$; b.p. 205–208°, $d^{17.5}$ 0·8554, n_D 1·4461, $[\alpha]_D + 12^0\,30'$. Its dextrorotatory form occurs in citronella oil, in balm oil, and in that of *Eucalyptus maculata* var. *citriodora* etc. (*Tiemann,* Ber. **29,** 904), while *l*-citronellal has been detected in "Java lemon olie". *Semicarbazone,* active, m.p. 84°; *d,l,* m.p. 96°. It can be identified as *α-citronellyl-β-naphthocinchonic acid,* m.p. 223°. One of its characteristic properties is the ease with which it undergoes ring closure to give isopulegol (p. 225), an alcohol isomeric with pulegol, the reduction product of pulegone (p. 235) (*Tiemann,* Ber. **30,** 27; *Prins,* Chem. Weekbl. **14,** 627; *Pickard,* J. **117,** 1248; *Horiuchi,* Mem. Kyoto **11,** 171). This takes place when it is treated with acetic anhydride or formic acid, or even on keeping (*Labbé,* Bull. **21** (1899), 1923; *Tiemann,* Ber. **32,** 825). Citronellal is reduced to citronellol (see above).

The acetal of citronellal is oxidised by $KMnO_4$ in aqueous solution to acetone and β-methyl-adipic mono-aldehyde, but in acetone about 80% of it is converted into a dihydroxy-aldehyde which, on further oxidation with CrO_3, yields first a hydroxy-dialdehyde and finally the keto-aldehyde *ω-aceto-β-methyl-hexanal* $MeCO{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CHMe{\cdot}CH_2{\cdot}CHO$ (*Harries*, Ber. **34**, 2981). When citronellal is oxidised with ozone, the products are acetone and β-methyl adipic acid from the terpinolene form, and ω-aceto-β-methyl-hexanal from the limonene form, so that the presence of both these forms in natural citronellal can be regarded as established (*Harries*, Ann. **410**, 10, 40; *Doeuvre*, Bull. **45** (1929), 1098; but cf. *Kuhn*, Ber. **65**, 1285).

A laevorotatory aldehyde closely related to citronellal, **rhodinal** (II) (*Barbier*, C. r. **122**, 673; **157**, 1114; *Bouveault*, Bull. **23** (1900), 463) b.p. 82–83°/8 mm which was formerly regarded as the terpinolene form of citronellal, is prepared by oxidising rhodinol (p. 201) (*Doeuvre*, Bull. **45** (1929), 1098; Parf. France **12**, 197; *Bogert*, Am. **52**, 4093). It differs from citronellal chiefly by forming under the influence of Ac_2O, not isopulegol, but the cyclic ketone menthone (p. 230); this reaction also takes place when rhodinol is oxidised with CrO_3. Rhodinal and menthone can be separated by means of the semicarbazone of the former (but cf. *Tiemann*, Ber. **30**, 38). The following formulae show the course taken in the two isomeric changes:



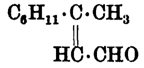
(I) Citronellal (limonene form) — Isopulegol — (II) Rhodinal (terpinolene form) — Menthone

The oxime of rhodinal undergoes a similar isomeric change into menthone-oxime with acetic anhydride. Conversely, isopulegol has been converted into citronellol by means of NaOEt, and into citronellal by heat (*Grignard*, C. r. **190**, 1164). When menthone is exposed to light in aqueous-alcoholic solution, the ring opens and an unsaturated aldehyde $C_{10}H_{18}O$ is formed; this is very similar to citronellal, but has a lower b.p. (195° as compared with 203–204° uncorr. for citronellal) (*Ciamician*, Ber. **42**, 1510). This aldehyde does not seem to be identical with the aldehyde obtained from menthone-oxime (p. 232) which is called "*mentho-citronellal*" by *Wallach* (Ann. **296**, 131). Rhodinal chlorohydrin has been used for the synthesis of *Tiemann's* irone (p. 127) (*Verley*, Bull. **2** (1935), 1205). For *hydroxy-citronellal*, which is industrially important because of its odour of lime-blossoms, see *Sornet*, Revue chim. ind. **37**, 74; *Fornet*, C. 1935 I 3860.

Citral, $C_{10}H_{16}O$, is a mixture of much of the terpinolene form $Me_2C{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CMe{:}CH{\cdot}CHO$ with a little of the limonene form $CH_2{:}CMe{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CMe{:}CH{\cdot}CHO$, b.p. 228–229°, b.p. 114·6–115·6°/15·5 mm, d_4^{17} 0·8897 (*Auwers*, J. pr. **84**, 14).

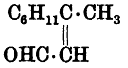
It is a pale yellow oil smelling of lemons; it occurs in lemon oil, verbena oil and abundantly in lemongrass oil, from which it is extracted commercially, and in many other essential oils. It is formed in the oxidation of geraniol (*Bouveault*, Bull. **3** (1908), 119) and has been synthesised by distilling *geranic acid* (see below) with calcium formate (*Tiemann*, Ber. **31**, 827). When the aldehyde group is reduced, a mixture of geraniol and nerol is obtained (*Ponndorf*, C. 1926 I 1983); catalytic hydrogenation gives various products according to the conditions: dihydro-citral (Germ.Pat. 298,193; *Skita*, Ber. **42**, 1634), tetrahydrocitral, tetrahydro-geraniol (*Ipatiev*, Ber. **45**, 3221) and 2,6-dimethyl-octane (*Skita*, Ber. **44**, 669). For synthetic *dihydrocitral* see Swiss P. 122,510–3, 123,448/9.

Natural citral consists of two geometrical isomers, *citral a* or *geranial* and *citral b* or *neral*, each of which is a mixture of the terpinolene and the limonene forms. For their configurations see *Kishner*, C. 1923 III 669.



$$\begin{array}{l} C_6H_{11}\cdot C\cdot CH_3 \\ \quad\;\; \| \\ \quad HC\cdot CHO \end{array}$$

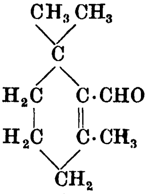
Citral a *(Geranial)*



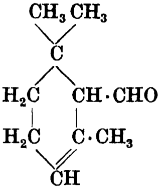
$$\begin{array}{l} C_6H_{11}C\cdot CH_3 \\ \qquad\; \| \\ OHC\cdot CH \end{array}$$

Citral b *(Neral)*

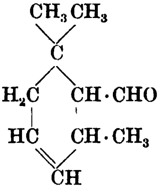
The two isomers can be separated by means of the different solubility of their *semicarbazones*, m.ps. *a* 164°, *b* 171°, or by their different reactivity towards cyanacetic acid, with which they condense to give the *citrylidene-cyanacetic acids*, viz. *geranylidene-cyanacetic acid* m.p. 122° and *nerylidene-cyanacetic acid* m.p. 95° (*Tiemann*, Ber. **22**, 115; **33**, 877). They can be converted into one another: citral *a* $\underset{\text{acid}}{\overset{\text{alkali}}{\rightleftarrows}}$ citral *b*. With β-naphthylamine and pyruvic acid citral condenses to give a characteristic derivative, *citryl-naphtho-cinchonic acid* (vol. IV), m.p. 197° (*Doebner*, Ber. **31**, 3195; *Tiemann*, Ber. **31**, 3324). Like cinnamaldehyde (vol. III), citral combines with bisulphites to give not only the normal bisulphite compound, but also salts of *tetrahydro-citral-disulphonic acid* by addition of 2 $NaHSO_3$ to the ethylenic double bonds. When boiled with aqueous sodium carbonate citral breaks down into methylheptenone (see above) and acetaldehyde (*Verley*, Bull. **17** (1897), 175), and it is oxidised by ozone to acetone, laevulinic aldehyde, and possibly glyoxal (*Harries*, Ber. **40**, 2823). When treated with $KHSO_4$, HI, AcOH and other reagents it loses water and gives cymene. Under special conditions it undergoes ring closure to *Δ^1-dehydro-isopulegol* (*Zeitschel*, J. pr. **133**, 370). Those derivatives of citral in which ring closure to cymene is impossible, such as citrylidene-aniline (Germ.Pat. 123,747), citrylidene-acetic acid, citrylidene-cyanacetic acid, citrylidene-acetoacetic ester, etc. give with conc. H_2SO_4 or H_3PO_4 (*Tiemann*, Ber. **33**, 3720) two derivatives of 2,6,6-Me_3-tetrahydro-benzaldehyde, α- and β-cyclocitral.



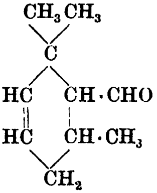
Δ^1- or
β-Cyclocitral



Δ^2- or
α-Cyclocitral



Δ^3-Cyclocitral

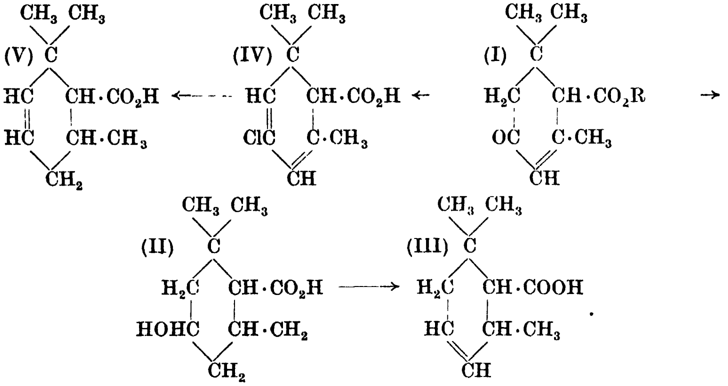


Δ^4-Cyclocitral

α-Cyclocitral, $C_{10}H_{16}O$, b.p. 75–77°/10 mm.; n_D^{18} 1·4744; d 0·925–0·930, *semicarbazone*, m.p. 204–206°, and **β-Cyclocitral**, b.p. 90–92°/10 mm.; n_D^{18} 1·4955; $d_4^{18.3}$ 0·9566 (*Kuhn*, Ber. **69**, 1555), *semicarbazone* m.p. 167°, *oxime* m.p. 84°, the products of this ring closure of citral derivatives, are also obtained by oxidising the cyclogeraniols (p. 203). β-Cyclocitral has also been prepared by partial catalytic reduction of safranal (p. 124) (*Kuhn*, Ber. **67**, 355). The percentage yield of α- and β-cyclocitral varies with the method of preparation; for their separation see Germ.Pat. 139,957 and *Kuhn*, Ber. **69**, 1155. Both α- and β-cyclocitrals are oxidised on standing in the air to the corresponding cyclogeranic acids (p. 207) and the β-compound is dehydrogenated by SeO_2 to give safranal in small yield (*Kuhn*, l.c.). For crystalline derivatives of cyclocitrals see *Neuberg*, Biochem. Z. **92**, 111. With acetone and NaOEt α-cyclocitral condenses to α-ionone, and β-citral to β-ionone (p. 125). **Pseudo-ionone,** $C_6H_{11}\cdot CMe:CH\cdot CH:CH\cdot CO\cdot Me$ b.p. 167–168°/23 mm. (*Tiemann*, Ber. **32**, 829; **33**, 882; *Auwers*, J. pr. **84**, 66), the condensation product of citral and acetone, undergoes a similar transformation under the action of conc. H_2SO_4 into the α- and β-ionones (p. 125) (*Hibbert*, Am. **46**, 119; Austrian P. 87,804). Methyl-pseudoionones see *Cherbulier*, Helv. **15**, 191. — *Methyl-ionone*, known commercially as *iraldein*, is prepared from α- and β-cyclocitral (*Koster*, J. pr. **148**, 249).

See further: *cyclodihydro-myrcene* (p. 200, *Semmler*, Ber. **34**, 3122), *cyclogeraniol* (p. 203), *cyclogeranic acid* (p. 207) and *cyclogeraniolene* (p. 95). *Citrylidene-malonic acid* is menthane-malonic-3-dilactone-1,4, see p. 139 (*Kuhn*, Ber. **64**, 1243).

Reference should be made to two other isomeric 2,6,6-trimethyl-tetrahydro-benzaldehydes, although they are not genetically related to citral. They are called Δ^3- and Δ^4-cyclocitrals, and they have been synthesised from *isophorone-carboxylic ester* (I) (p. 139). This ester is reduced with Na + EtOH to a mixture of geometrically isomeric hydroxy-acids (II), which lose water and give *Δ^3-cyclogeranic acid* (III). With PCl_5 isophorone-carboxylic ester is converted into *δ-chloro-cyclogeranioladiene-carboxylic acid* (IV), from which, together with the Δ^2- and Δ^3-acids, *Δ^4-cyclogeranic acid* (V) is obtained by reduction.



The Δ^3- and Δ^4-cyclogeranic acids so prepared are converted, by the method described on p. 207, into **Δ^3-cyclocitral** b.p. 76°/12 mm. and **Δ^4-cyclocitral.** For isomeric *trimethyl-tetrahydro-benzaldehydes* see Germ. Pat. 141,973, 142,129. Δ^1- and Δ^2-Cyclogeranic acids see next page.

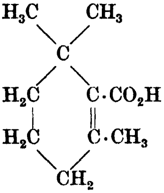
(4) Olefinic Terpene Acids

Citronellic acid, $C_{10}H_{18}O_2$, is a mixture of $CH_2:CMe\cdot CH_2CH_2CH_2CHMe\cdot CH_2COOH$ and $Me_2C:CH\cdot CH_2CH_2CHMe\cdot CH_2COOH$, b.p. 143·5°/10 mm. (*Harries*, Ber. **41**, 2197). It can be prepared from its nitrile, which is obtained by dehydrating citronellal oxime (*Zimmerman*, Rec. **50**, 283). It is also produced by oxidising citronellal, into which it can be reconverted by distilling its calcium salt with calcium formate. It occurs in lemongrass oil, etc. (*Naves*, Parfums **9** (1931), 60) and its *d,l*-form is found in camphor oil (*Rochussen*, J. pr. **105**, 120). It is formed in the electrolytical reduction of geranic acid (*Penfold*, Proc. Roy. Soc. N.S.W. **68**, 80) and its optically active forms can be converted by catalytic reduction into optically active *tetrahydrogeranic acid* (Germ.Pat. 298,193). Just as citronellol can be converted into rhodinol, so citronellic acid undergoes rearrangement into *rhodinic acid* when its esters are treated with HCl (*Barbier*, C. r. **157**, 1114). Rhodinic acid is also obtained by oxidising rhodinol with chromic acid. *d, l*-Rhodinic acid results also from the reduction of geranic acid with Na and amyl alcohol (*Tiemann*, Ber. **31**, 2899). Rhodinic ester itself, when reduced with Na + EtOH, gives *d, l*-rhodinol (p. 201).

Geranic acid, $C_{10}H_{16}O_2$, a mixture of $(CH_3)_2C{:}CH\cdot CH_2\cdot CH_2\cdot C(CH_3){:}CH\cdot COOH$ and $CH_2{:}C(CH_3)\cdot CH_2\cdot CH_2\cdot CH_2\cdot C(CH_3){:}CH\cdot COOH$, b.p. 153°/11 mm., occurs in lemongrass oil (*Naves*, C. 1931 II 330) and is prepared by oxidising citral, or synthetically from methyl heptenone (p. 203) with iodo-acetic ester or bromo-acetic ester and zinc (*Barbier*, C. r. **122**, 393; *Tiemann*, Ber. **31**, 825). Sulphuric acid converts it into the isomeric hydroaromatic *cyclogeranic acid* (see below). When heated at ordinary pressure, it gives *geraniolene* C_9H_{16} (*Auwers*, Ann. **387**, 183; *Grignard*, Bull. **45** (1929), 809), which is converted by the action of sulphuric acid into the isomeric *cyclogeraniolene* (p. 95) (*Auwers*, ib. 185). For the catalytic reduction of geranic acid and its detection see Germ. Pat. 248,193, and *Simonsen*, Proc. Roy. Soc. N.S.W. **68** (1935), 80; for refractometric data *Auwers*, Ann. **432**, 87. *Dehydrogeranic acid* $C_{10}H_{14}O_2$, $CMe_2{:}CH\cdot CH{:}CH\cdot CMe{:}CH\cdot COOH$, m.p. 186°, occurs in nature (*Cahn*, J. **1931**, 3134) and has been synthesized from 2-methylbutenal $Me_2C{:}CH\cdot CHO$ (*F. G. Fischer*, Ann. **494**, 263; Ber. **68**, 1726).

α-Cyclogeranic acid, $C_{10}H_{16}O_2$, formula (II), m.p. 106°, b.p. 138°/11 mm., *amide* m.p. 121°, is formed together with the β-acid when geranic acid is treated with 65–70% sulphuric acid below 0°, and is best prepared by heating geranic acid with anhydrous formic acid (*Bernhauer*, *Forster*, J. pr. **147**, 199). Its diphenyl-amidine is reduced by Na + EtOH to cyclocitrylidene-dianiline, and this is converted by dilute mineral acids into a mixture of α- and β-cyclocitral (*Merling*, Ber. **41**, 2064, 2066). Its constitution is proved by its hydrogenation on Pd to 1,3,3-trimethyl-cyclohexane-2-carboxylic acid m.p. 82–83° (*Wallach*, Ann. **418**, 57), and by its degradation to α-acetyl-β,β-dimethyl-adipic mono-ester and β,β-dimethyl-adipic acid (*Tiemann*, Ber. **31**, 828; **33**, 3713). For its behaviour towards HgO + I_2, see *Bougault*, C. r. **150**, 397.

β-Cyclogeranic acid, $C_{10}H_{16}O_2$, formula (I), m.p. 93–94°, *amide* m.p. 202°, is formed together with the α-form by the ring closure of geranic acid described above (*Tiemann*, Ber. **33**, 3708), and also very easily by oxidising β-cyclocitral; it can be reconverted into the latter through the diphenylamidine and cyclocitrylidene-dianiline $C_6H_{15}\cdot CH{:}(NHPh)_2$ (*Merling*, Ber. **41**, 2064, 2066).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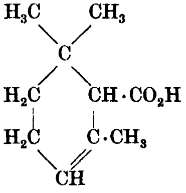

II

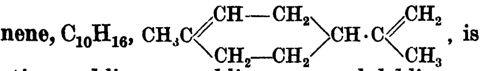
Δ³-Cyclogeranic acid, *2,6,6-trimethyl-Δ³-tetrahydrobenzoic acid*, m.ps. α 76° and β 84°, from hydroxy-dihydro-cyclogeranic acid, has been used for the preparation of Δ³-cyclocitral (p. 206) (*Merling*, Ber. **41**, 2066).

B. MONOCYCLIC TERPENE OR MENTHANE GROUP

1. HYDROCARBONS

This group includes various terpenes, some of which are optically active and others inactive or racemic mixtures: examples are *limonene*, *dipentene*, *terpinolene*, the α-, β- and γ-*terpinenes*, α- and β-*phellandrene*, all of which are dihydro-*p*-cymenes, and *sylvestrene* and *carvestrene*, which are dihydro-*m*-cymenes. The close relationship of the various terpenes is shown by their interconversions and rearrangements, and the majority of them has been prepared synthetically (cf. p. 198).

(a) THE LIMONENE AND DIPENTENE GROUP



Limonene, $C_{10}H_{16}$, $CH_3C\begin{matrix}\diagup CH—CH_2 \diagdown \\ \diagdown CH_2—CH_2 \diagup\end{matrix}CH\cdot C\begin{matrix}\diagup CH_2 \\ \diagdown CH_3\end{matrix}$, is known in three modifications: *d*-limonene, *l*-limonene and *d, l*-limonene or dipentene.

d-Limonene, formerly also called *citrene*, *hesperidene*, *carvene*, is, together with pinene, one of the most widely distributed terpenes. It is present in the oil obtained from the skin of the fruits from *Citrus aurantium*, *Citrus sinensis* and other citrus species, in the oils of bergamot, lemon, caraway, dill, celery, etc. B.p. 176^0, b.p. 71^0/20 mm; d_4^{25} 0·8409; n_D^{14} 1·4725; $\alpha_{D_{20}}$ + 126^0 8·4′ (*v. Braun*, Ber. **56**, 1563; *Padmanabhan*, Am. **57**, 334) **l-Limonene** is found in the oil extracted from the Douglas fir (*Pseudotsuga* spp.) and from the silver fir (*Abies pectinata*), in elemi oil, Russian peppermint oil, in certain kinds of turpentine etc. B.p. 176^0, $[\alpha]_D$ — 123·7^0 (*Dupont*, Bull. **35** (1924), 625), d_4^{15} 0·8460. See p. 239 and *Tchugaev*, Ber. **33**, 735 for the preparation of *l*-limonene from *d*-carvone.

Both limonenes are liquids with a pleasant smell of lemons. They differ from each other, as do their derivatives, only in the direction of their optical rotation. The two active limonenes combine with dry bromine to give *tetrabromides* melting at 104^0, and having equal but opposite rotations of about $[\alpha]_D = 74^0$ (*v. Braun*, Ber. **56**, 1562). Both optically active limonenes give with moist hydrogen halides the addition products of *d, l*-limonene or dipentene. If dry HCl is passed through a solution of limonene in CS_2, a monohydrochloride is obtained which can be reduced with Na + EtOH in the cold to *carvomenthene* (p. 214) and which gives optically active α-terpineol when treated with dilute alkali or sodium acetate (*Semmler*, Ber. **36**, 1036; *Wallach*, Ann. **252**, 144). In the catalytic hydrogenation with H_2 on Ni as well as on Pd the first stage consists in saturating the double bond in the side chain, with the formation of *carvomenthene* (p. 214). In a second stage the fully saturated *menthane* (p. 215) is formed (*Vavon*, C. r. **158**, 409; *Kern*, Am. **47**, 1147). Dipentene behaves in the same way (*Armstrong*, Proc. Roy. Soc. **108**, 121). Oxidation with perbenzoic acid takes the opposite course, attacking the ring double bond first and producing, from *d*-limonene, *d*-limonene-1,2-oxide, which has been converted, first into $\Delta^{8(9)}$-menthene-1,2-diol, then into menthane-1,2-diol, and finally into *d-tetrahydro-carvone* (p. 232) (*Meerwein*, J. pr. **113**, 9). In the autoxidation of limonene both double bonds remain intact and *d, l-carveol* (p. 227) and *d, l-carvone* (p. 238) are formed (*Blumann*, Ber. **47**, 2623). Ozonisation gives a normal ozonide, in which both double bonds are saturated; when this is decomposed and oxidised with CrO_3, *β*, *δ*-diacetylvaleric acid $C_9H_{14}O_4$ is obtained (*Harries*, Ber. **49**, 1035; C. 1916 II 994). By gentle oxidation with $KMnO_4$ limonene is converted into the tetrahydric alcohol *limonetritol* $C_{10}H_{16}(OH)_4$ (p. 223). When the optically active limonenes are heated to a high temperature, dipentene and substances of high molecular weight are formed. For the behaviour of limonene towards CrO_2Cl_2 see *Sword*, Chem. News **133**, 1; towards H_2O_2 in AcOH, id. J. **127**, 1632.

The *nitrosochlorides* of the limonenes deserve particular attention (*Wallach*, Ber. **28**, 1308; *Baeyer*, Ber. **29**, 10; *Leach*, J. **87**, 413). *d*- and *l*-Limonene form two nitrosochlorides each, which differ physically though not chemically, and which yield isomeric *nitrolamines* with bases and *nitrosocyanides* with KCN.

α, *d*- and *l*-**Limonene nitrosochloride,** m.p. 103^0, $[\alpha]_D = \pm 313^0$.
β, *d*- and *l*-**Limonene nitrosochloride,** m.p. 105^0, $[\alpha]_D = \pm 240^0$.

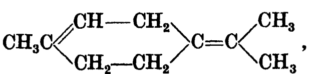
All the four nitrosochlorides, when heated with sodium methoxide, give *carvoxime*, m.p. 72^0 (p. 239), the *l*-limonene nitrosochlorides giving the *d*-oxime, and the *d*-nitrosochlorides the *l*-oxime (see also *Deussen*, Ber. **43**, 519).

d, l-**Limonene, dipentene,** *cinene,* b.p. 175–176°, d_4^{20} 0·8390, $n_D^{?}$ 1·4724. Dipentene is the principal constituent of the oil from *Euthamia caroliniana* (*Russell,* Am. **38,** 1398) and occurs in camphor oil, in lemongrass oil, in the essential oil from *Euthamia caroliniana* (*Russell,* Am. **38,** 1398), in sulphate-turpentine oil (*Halse,* Ber. **50,** 627), in bergamot oil and other citrus oils (*Holtz,* Chem. Weekbl. **17,** 674; **18,** 108, 302) and in many other essential oils. It is formed when *d*-limonene, *l*-limonene, pinene or camphene are heated to 250–300° and is therefore present in the Russian and Swedish so-called "turpentine oils" which are extracted at higher temperatures. It is produced when caoutchouc is distilled ("*kautschin*") (*Staudinger,* Helv. **5,** 785; **9,** 549) and is a polymerisation product of the isoprene C_5H_8 (p. 345) formed in that distillation, together with other isomers and polymers (*Wallach,* Ann. **227,** 295; *Lebedev,* C. 1918 I 1003; cf. diprene, *Bell,* J. **1927,** 1695). It is further obtained by mixing equal parts of *d*- and *l*-limonene, and from pinene by the action of acids or by heating under pressure (*Knecht,* J. Dyers **41** (1926), 356; *Kondakov,* Parf. **19** (1926), 212). It is a dehydration product of linalool or terpin hydrate (p. 202 and 219) (*Ono,* Bull. chem. Soc. Japan **1** (1926), 248), α-terpineol (p. 223) and cineole, (p. 220) (id. ib. **2** (1927), 207). The synthesis of dipentene from the elements has been achieved through the synthesis of α-terpineol (p. 223), from which it is obtained by heating with potassium bisulphate (p. 138) (*Perkin,* J. **85,** 654).

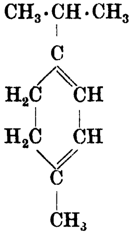
Pure dipentene is prepared by heating its dihydrochloride with aniline, or with sodium acetate in AcOH. Pure dipentene is a liquid with a pleasant smell of lemons. Although more stable than most of the other terpenes, it undergoes isomeric change into terpinene (p. 210) when treated with alcoholic sulphuric acid or hydrochloric acid. Dipentene is dehydrogenated by conc. sulphuric acid, or phosphorus pentasulphide, or by heating with sulphur (Brit.Pat. 206,248) and gives p-cymene. Bromination of its dihydrobromide, followed by reduction also yields p-cymene (*Baeyer,* Ber. **31,** 1402). The derivatives of dipentene can be obtained not only from dipentene, but also by mixing equal parts of the *d*- and *l*-limonene derivatives.

trans-**Dipentene dihydrochloride,** $C_{10}H_{18}Cl_2$, m.p. 50°, b.p. 110–112°/10 mm., from limonene, dipentene, pinene, Δ^3-carene (p. 246) (*Dupont,* Ann. chim. (10), **1,** 184) with HCl; cis-**dipentene dihydrochloride,** m.p. about 25°, from cineole with HCl + AcOH cooled with ice; trans-**dipentene dihydrobromide,** $C_{10}H_{18}Br_2$, m.p. 64° from limonene, dipentene, or terpin (p. 219) with HBr. cis-**Dipentene dihydrobromide,** $C_{10}H_{18}Br_2$, m.p. 38–40°, is formed, together with the trans form, by the action of HBr upon a cooled solution of cineole in AcOH; see also cis-terpin. **Tetrahydro-dipentene tribromide,** *tribromomenthane* $C_{10}H_{18}Br_3$, m.p. 110°, from trans dipentene dihydrobromide with bromine and AcOH. **Dipentene tetrabromide,** $C_{10}H_{16}Br_4$, m.p. 124°; **dipentene dihydroiodide,** $C_{10}H_{18}I_2$, m.p. 77–79° (*Baeyer,* Ber. **26,** 2864; **27,** 443; *Wallach,* Ann. **239,** 13; **264,** 25; **281,** 140, 143).

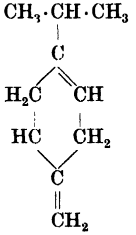
α-**Dipentene nitrosochloride,** $C_{10}H_{16}(NO)Cl$, m.p. 103–104°; see carvoxime p. 239 (*Wallach,* Ann. **270,** 175).

Terpinolene,  $\mathrm{CH_3C}\begin{array}{l}\diagup\mathrm{CH{-}CH_2}\diagdown\\ \diagdown\mathrm{CH_2{-}CH_2}\diagup\end{array}\mathrm{C{=}C}\begin{array}{l}\diagup\mathrm{CH_3}\\ \diagdown\mathrm{CH_3}\end{array}$, b.p. 185–187°, has not yet been identified in essential oils with certainty (but see *Clover,* Am. **39,** 613). It is formed when terpin hydrate, terpineol or cineole is heated with dilute H_2SO_4, and when pinene is treated with the concentrated acid. It can be prepared by treating α-terpineol (m.p. 35°) with hot aqueous oxalic acid, and the best method is to treat γ-terpineol (m.p. 69°) with anhydrous formic acid (*Wallach,* Ann. **275**, 106; **368**, 11), although, because of its instability, it is very doubtful whether pure terpinolene has ever been obtained (see *Marot*, Bull. Pin **1938**, 38). Terpinolene combines with bromine to give a *dibromide* $C_{10}H_{16}Br_2$, m.p. 70°, and a *tetrabromide*, $C_{10}H_{16}Br_4$, m.p. 116° (*Baeyer*, Ber. **27**, 447), from which it can be regenerated in a state of great purity by reduction with zinc dust and alcohol. It adds on hydrogen halides to give dipentene dihydrohalides. Terpinolene is one of the least stable terpenes and readily undergoes rearrangement in the presence of acids, the semicyclic double bond migrating into the ring with the formation of *terpinene.*

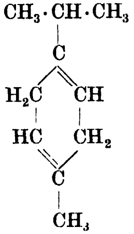
(b) THE TERPINENE GROUP. — The name terpinene is used for the three following dihydro-cymenes (*Wallach*, Ann. **374**, 224):



α-Terpinene



β-Terpinene



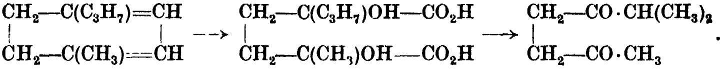
γ-Terpinene

Of these, the α- and γ-terpinenes have been found in essential oils, while β-terpinene has hitherto only been prepared synthetically. Both the natural terpinene and the terpinene artificially prepared from other terpenes or terpene alcohols are in general a mixture of various amounts of α- and γ-terpinenes, in which α-terpinene usually predominates. In chenopodium oil only α-terpinene (*carvenene*) seems to be present (*Nelson*, Am. **42**, 1204; *Henry*, J. **119**, 1714; **127**, 1649), and in Spanish thyme oil (*Schimmel & Co.*, Report **1922**, 69) and in samphire oil from *Crithmum maritimum* (*Richter*, Ber. **60**, 477) only γ-terpinene (*isocarvenene*). A hydrocarbon $C_{10}H_{16}$, b.p. 174°, which seems to consist essentially of γ-terpinene, can be obtained from succino-succinic ester (p. 146) by rearrangement into 1-methyl-4-isopropyl-cyclohexadione-2,5, followed by reduction and elimination of water (*Baeyer*, Ber. **26**, 232; *Harries*, Ber. **35**, 1170).

Terpinene (α + γ), b.p. 179–181°, d^{20} 0·846 (*Auwers*, Ber. **42**, 2425), when pure, has an odour resembling lemons and is optically inactive. It has been detected in cardamom oil, elemi oil, coriander oil, ajowan oil from *Carum copticum* and *C. Ajowan*, of which the latter is particularly rich in γ-terpinene (*Richter*, Ber. **60**, 477). Artificially it is produced by boiling dipentene, phellandrene, terpinolene, sabinene, terpin hydrate, cineole, terpineol,. or dihydrocarveol with dilute alcoholic sulphuric acid, or by shaking pinene with a little conc. sulphuric acid (*Murayama*, J. Pharm. Soc. Japan **1923** No. 498,46). Products rich in α-terpinene are obtained: (1) by reducing *chlorocarvenene*, from carvenone (p. 234) and PCl_5, with Na + EtOH (*Semmler*, Ber. **42**, 4171); (2) from *carvenyl-amine* (p. 228) by loss of NH_3 (*Harries*, Ber. **41**, 2516; *Morell*, Ann. **410**, 75); (3) from methyl-dichloromethyl-ketodihydrobenzene (p. 119) with isopropyl-MgI, and heating the resulting compound with alcoholic potash (*Auwers*, Ber. 48, 1366). The last method is a complete nuclear synthesis of α-terpinene and seems to yield the pure α-form. α-Terpinene from terpinene dihydrochloride has the following constants: b.p. 173·5–174·8°/755 mm., $d_4^{19,6}$ 0·8375, $n_D^{19,7}$ 1·477; pure γ-terpinene has b.p. 183°/760 mm., d_4^{15} 0·853, $n_D^{14.5}$ 1·4765 (*Richter*, Ber. **63**, 1717, 1720); *maleic acid adduct* of α-terpinene m.p. 60—61° (*M. Lipp*, J. pr. **149**, 120).

A very characteristic derivative of α-terpinene is **terpinene nitrosite,** $C_{10}H_{15}(NO_2)(:NOH)$, m.p. 155°, which is obtained by the addition of KNO_2 to a solution of terpinene in AcOH; it is used for detecting α-terpinene in essential oils. It is monomolecular and insoluble in alkalies, but with bases gives nitrolamines which dissolve in alkalies, e.g. with ammonia, **terpinene nitrolamine,** $C_{10}H_{15}(NOH)\cdot NH_2$, m.p. 118° (*Wallach*, Ann. **241**, 320; *Wieland*, ib. **424**, 92). Among the products of the catalytic hydrogenation of α-terpinene nitrosite 1,2-diamino-hexahydrocymene has been identified (*Wieland*, Ann. **424**, 95), and this has been considered as evidence for the constitutional formula given above. γ-Terpinene, when sufficiently pure, yields a *nitrosochloride* m.p. 111°, converted by alkali into *2-azoxy-p-cymene* m.p. 52–53° (*Richter*, Ber. **60**, 477). *Nitrol-piperidide* m.p. 149°, *nitrosate* m.p. 116°.

On oxidation with potassium permanganate, *a*-terpinene gives *α, α′-dihydroxy-α-methyl-α′-isopropyl-adipic acid*, m.p. 189°, which can be further broken down to ω-dimethyl-acetonylacetone; the latter compound is also the product of the ozonisation of α-terpinene (*Wallach*, Ann. **362**, 293; *Auwers*, Ber. **48**, 1366):



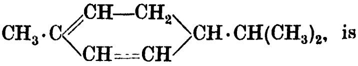
$$\begin{array}{l} CH_2-C(C_3H_7)=CH \\ \vert \qquad\qquad\qquad\quad \vert \\ CH_2-C(CH_3)=CH \end{array} \dashrightarrow \begin{array}{l} CH_2-C(C_3H_7)OH-CO_2H \\ \vert \\ CH_2-C(CH_3)OH-CO_2H \end{array} \longrightarrow \begin{array}{l} CH_2-CO\cdot CH(CH_3)_2 \\ \vert \\ CH_2-CO\cdot CH_3 \end{array}.$$

β-Terpinene, b.p. 173–174°, *d* 0·838 has been prepared from the condensation product of sabinaketone (p. 240) with bromo-acetic ester and zinc, by removal of water and distillation of the resulting unsaturated acid $C_9H_{14}:CH\cdot CO_2H$, m.p. 68°. It unites with bromine to a crystalline *tetrabromide* m.p. 155°, while γ-terpinene yields a *tetrabromide* m.p. 128° (*Richter*, Ber. **63**, 1714) and α-terpinene only seems to form a liquid addition product with bromine (*Wallach*, Ann. **362**, 285; *Schimmel & Co.*, Report **1922**, 68).

γ-Terpinene gives with $KMnO_4$ an *erythritol* $C_{10}H_{16}(OH)_4$, m.p. 237°, which is converted into a mixture of thymol and carvacrol when treated with dilute H_2SO_4 (*Gildemeister*, C. 1909 II 2159).

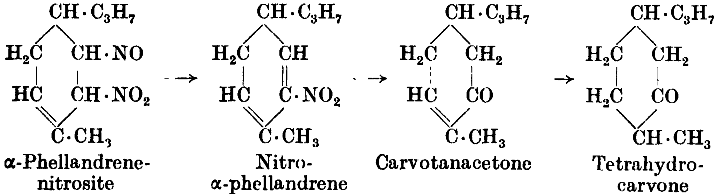
Terpinene Dihydrohalides.—All three terpinenes unite with two molecules of hydrogen halide to form well-defined terpinene dihydrohalides, from which a mixture of α- and γ-terpinene is regenerated by heating with aniline or alcoholic potash. The dihydrohalides are converted into *terpinene-terpin* (p. 221) and *terpinenol*-4 (p. 224) by shaking with dilute alkalies, and these compounds are isomeric with terpin and α-terpineol which are obtained from the dipentene dihydrohalides by a similar reaction. The terpinene dihydrohalides resemble the corresponding dipentene derivatives in occurring in two geometrically isomeric forms, of which only the trans compounds are a solid at room temperature. They can be obtained, not only from the terpinenes, but with great ease by the action of the hydrogen halides on the bicyclic hydrocarbons, sabinene and thujene (p. 241), and by treating terpinene-terpin (p. 221) and the terpinenols (p. 224) with a hydrogen halide in AcOH. trans-**Terpinene dihydrochloride, dihydrobromide,** and **dihydriodide** melt at 52°, 59° and 77°. A **terpinene monohydrochloride,** $C_{10}H_{17}Cl$, b.p. 87–92°/12 mm., can be obtained from terpinene and sabinene with completely dry HCl in CS_2. It corresponds to terpinenol-4 (p. 224), since it is reduced by Na and alcohol to *carvomenthene* (p. 214) (*Semmler*, Ber. **40**, 2959).

(c) THE PHELLANDRENE GROUP. — α- and β-Phellandrene are two isomeric dihydro-p-cymenes, which have the distinctive property of combining very easily with nitrous acid to give well characterised pseudo-nitrosites (nitrites) (p. 199). The phellandrenes are two of the most unstable terpenes and are easily converted into other terpenes, such as dipentene and terpinene, by the action of acids. Their addition products with bromine and the hydrogen halides are all liquids, and since they cannot be regenerated from the crystalline pseudo-nitrosites, they have not yet been obtained in a pure state.

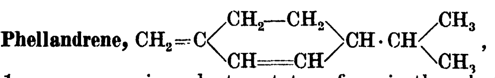
α-Phellandrene, $C_{10}H_{16}$, 
$CH_3\cdot C\overset{CH—CH_2}{\underset{CH=CH}{\langle\qquad\rangle}}CH\cdot CH(CH_3)_2$, is optically active and has been found fairly often in essential oils, both in its dextrorotatory and its laevorotatory forms. *d*, α-Phellandrene has been isolated from the oil of bitter fennel (*Foeniculum vulgare*), oil of elemi (*Wallach*, Ann. **246**, 233), schinus, and ginger grass oils; *l*, α-phellandrene in Australian eucalyptus oil from *Eucalyptus amygdalina* and in Chinese star aniseed oil from *Illicium verum*. *dl*, α-Phellandrene has been synthesised from the condensation product of 4-isopropyl-Δ^2-cyclohexenone (p. 115) and MeMgI by loss of water (*Wallach*, Ann. **246**, 233; **359**, 285; *Read* et al., J. **1936**, 1595) and it is also formed together with *d*, *l*-piperitol by treating *d*, *l*-piperityl-trimethylammonium iodide with Ag_2O and water (*Read*, J. **1930**, 2770; *Sherwood*, J. **1931**, 3340). *d*, α-Phellandrene is obtained from chloro-phellandrene, the product of the action of PCl_5 upon carvotanacetone (p. 234), by reduction with Na + EtOH (*Harries*, Ber. **38**, 1832; *Read*, l. c.). On oxidation with $KMnO_4$, α-phellandrene gives α-hydroxy-β-isopropyl-glutaric and isopropyl-succinic acids. It is reduced to *carvomenthene* (p. 214) by Na + EtOH (*Semmler*, Ber. **36**, 1749) Unlike β-phellandrene it does not give a crystalline nitrosochloride (*Francesconi*, Gazz. **46** I 119). It is a poison paralysing the heart (*Mac Pherson*, Med. Australia **2** (1927), 108).

Dihydroxy-phellandrene, $C_{10}H_{18}O_2$, m.p. 168°, has been detected in the essential oil of Manila elemi resin (*Mladenović*, Mo. **64**, 177; Bull. Youg. **5**, (1936), 142).

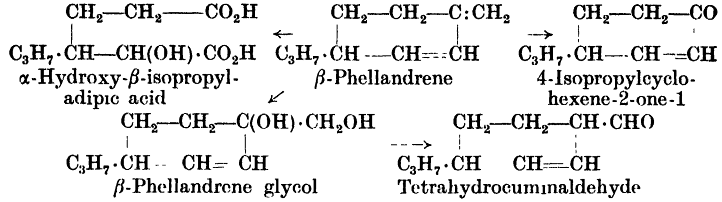
The bimolecular α-phellandrene nitrite obtained with nitrous acid (see below) is known in two forms which are probably geometrical isomers: *α-phellandrene-α-nitrosite* m.p. 120–121° (*Smith*, J. **125**, 930) and *α-phellandrene-β-nitrosite*, m.p. 105°. Both, when reduced with zinc and AcOH, give *α-phellandrene-diamine* $C_{10}H_{16}(NH_2)_2$ b.p. 133°/17 mm., which shows that both nitrogen atoms are linked to carbon. It does not give nitrolamines with bases, like the normal nitrosites. With sodium alcoholate it loses hyponitrous acid and forms *nitro-α-phellandrene*, b.p. 125–129°/9 mm., which can be reduced with zinc and glacial acetic acid to active *carvotanacetone*, and with sodium and alcohol to *tetrahydrocarvone* (*Wallach*, Ann. **336**, 9) and *carvomenthol* (*Paolino*, Lincei **30** II 265, 313).



α-Phellandrene-nitrosite (bimolecular) — Nitro-α-phellandrene — Carvotanacetone — Tetrahydrocarvone

β-Phellandrene, 
$CH_2{=}C\overset{CH_2—CH_2}{\underset{CH=CH}{\langle\qquad\rangle}}CH\cdot CH\overset{CH_3}{\underset{CH_3}{\langle}}$, b.p. 169–171°, b.p. 57°/11 mm., occurs in a dextrorotatory form in the oil of water fennel from *Phellandrium aquaticum* (*Francesconi*, Gazz. **46** I 119; *Nelson*, Am. **42**, 1286) and in small quantity in schinus oil, together with α-phellandrene. It oxidises very readily in the air, splitting off the semicyclic CH_2 group and giving 4-isopropyl-cyclohexene-2-one-1 (*Wallach*, Ann. **348**, 29). On oxidation with a very dilute permanganate solution a *glycol*, $C_{10}H_{16}(OH)_2$, b.p. 150°/10 mm., is formed, which on treatment with dilute sulphuric acid yields tetrahydro-

cuminaldehyde, together with a dihydrocuminalcohol. More energetic action of $KMnO_4$ gives α-hydroxy-β-isopropyl-adipic acid:



α-Hydroxy-β-isopropyl-adipic acid ← β-Phellandrene → 4-Isopropylcyclohexene-2-one-1

β-Phellandrene glycol ⇢ Tetrahydrocuminaldehyde

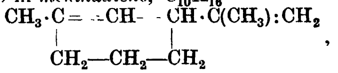
This tetrahydrocuminaldehyde—the position of the double bond is not quite certain (*Wallach*, Ann. **340**, 15)—seems to be identical with phellandral (p. 229), which occurs in nature together with β-phellandrene (*Penfold*, J. **121**, 266).

β-Phellandrene nitrite $C_9H_{14}(NO)CH_2NO_2$, bimolecular (p. 199), m.p. 98° (β-nitrosite) and 102° (α-nitrosite), is obtained by the action of nitrous acid and is reduced by zinc and AcOH to *β-phellandrene-diamine*, b.p. 134°/11 mm., and by Na and EtOH to cuminaldehyde. It is converted by NaOEt into *nitro-β-phellandrene* $C_{10}H_{15}NO_2$, and this is reduced by zinc and AcOH to dihydrocuminaldehyde (*Wallach*, Ann. **340**, 1). In contrast to α-phellandrene, β-phellandrene forms a crystalline *nitrosochloride*, the two stereoisomeric forms of which melt at 101–102° and 100°; they are decomposed by AcOH into $\Delta^{2,6}$-dihydrocuminaldehyde, carvacrol and cuminaldehyde (*Francesconi*, Gazz. **46** I 119).

$\Delta^{3,8(9)}$-p-Menthadiene, $C_{10}H_{16}$, b.p. 184°, has been synthesized from Δ^3-tetrahydro-p-toluic ester with MeMgI (*Perkin*, *Wallach*, J. **97**, 1427; *Semmler*, Ber. **39**, 2585). It is formed in the reduction of pulegone (*Read*, J. **1934**, 242), and, together with **$\Delta^{2,8(9)}$-p-menthadiene,** b.p. 173°, by pyrolysis of 3,8-dihydroxy-p-menthane (*Doeuvre*, Bull. **53** (1933), 170).

(d) **THE SYLVESTRENE GROUP** comprises **sylvestrene,** which is optically active, and **carvestrene,** the *d,l*-form of the former. Both carry the methyl and isopropyl groups in the meta positions of the 6-ring, and are, therefore, derivatives of m-dihydrocymene. Because of the position of the double bonds and side chains and of their reactions sylvestrene and carvestrene might be called the limonene and the dipentene of the m-dihydrocymene series.

Sylvestrene, $\Delta^{1,8(9)}$-m-*menthadiene*, $C_{10}H_{16}$



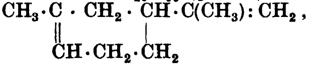
$$\begin{array}{l} CH_3{\cdot}C{=}{=}CH{-}{-}CH{\cdot}C(CH_3){:}CH_2 \\ \quad | \qquad\qquad\qquad | \\ \quad CH_2{-}CH_2{-}CH_2 \end{array},$$

b.p. 176°, does not seem to occur in nature, but is formed from the Δ^3- and Δ^4-carene present (p. 246) during the process of extracting it from the essential oils (*Simonsen*, *Rao*, J. **123**, 549; **127**, 2494; *Aschan*, Svensk Kem. Tidskr. **39** (1927), 165; *Semmler*, Ber. **60**, 1591; *Aschan*, Ann. **461**, 1). Both a dextrorotatory (*Wallach*, Ann. **252**, 149) and a laevorotatory form (*Schimmel*, Report April **1914**, 51; *Czerny*, C. 1924 II 674) are known. Sylvestrene possesses a pleasant smell of lemons. Both forms have been synthesised by *Perkin* (J. **103**, 2225) by treating *d*- and *l*-Δ^3-tetrahydro-m-toluic esters (p. 132) with MeMgI, and removing water. Addition of conc. H_2SO_4 to a solution of sylvestrene in Ac_2O gives a deep blue colour (*Herzenberg*, Ber. **58**, 2261). Carvestrene and dihydrobenzene (p. 96) behave in the same way, while other terpenes give a red or orange colour under these conditions.

Sylvestrene is one of the most stable of terpenes, and cannot be transformed into isomeric terpenes either by heat or by acids (*Wallach*, Ann. **239**, 28). On bromination of its dihydrobromide and subsequent reduction with zinc dust and HCl, m-cymene is obtained, while limonene, treated similarly, gives p-cymene (see above). Sylvestrene is, therefore, the limonene of the m-dihydrocymene series. Like limonene, it forms dihydrohalides by addition of two molecules of hydrogen halides, but these, in contrast to the corresponding limonene derivatives, are optically active, and active sylvestrene can be regenerated from them by heating with aniline or sodium acetate. When the dihydrohalides are treated with dilute caustic potash, alcohols are formed which correspond to terpin and terpineol, viz. *sylveterpin*, $C_{10}H_{18}(OH)_2$, m.p. trans 136°, cis 70–75°, and *sylveterpineol*, $C_{10}H_{17}(OH)$ b.p. 210° (*Haworth, Perkin, Wallach*, Ann. **399**, 155); *dihydrochloride* $C_{10}H_{18}Cl_2$, m.p. 72–73°; *dihydrobromide*, m.p. 72°; *dihydriodide*, m.p. 67°. *Tetrabromide* $C_{10}H_{16}Br_4$, m.p. 135°; *nitrosochloride* $[C_{10}H_{16}(NO)Cl]_2$, m.p. 107° (*Wallach*, Ann. **252**, 150).—Catalytic hydrogenation of sylvestrene gives m-menthane (p. 216).

Carvestrene, $C_{10}H_{16}$, b.p. 178°, is formed in the distillation of carylamine hydrochloride (p. 248); it is the racemic form corresponding to the active sylvestrene, and since it can be converted into m-cymene, it is the dipentene of the m-dihydrocymene series (*Baeyer*, Ber. **27**, 3485; **31**, 1405). For its blue colour with H_2SO_4, see sylvestrene. It has been synthesised from rac.-Δ^2-tetrahydro-m-toluic ester (*Haworth, Perkin*, J. **91**, 480; **103**, 2225). The *dihydrochloride*, also obtained by mixing *d*- and *l*-sylvestrene dihydrochlorides, m.p. 52–53° (*Simonsen*, J. Ind. ch. Soc. **9** (1926), 133). *Dihydrobromide*, m.p. 48–50°. *Carveterpin*, m.p. trans 127°, cis 94°.

Diprene, $\Delta^{6,8(9)}$-m-*Menthadiene*, $C_{10}H_{16}$ (p. 345)



$$\begin{array}{l} CH_3\cdot C\cdot CH_2\cdot CH\cdot C(CH_3){:}CH_2, \\ \quad \| \qquad\qquad\quad | \\ CH\cdot CH_2\cdot CH_2 \end{array}$$

b.p. 175°, the polymerisation product of isoprene at ordinary temperature, gives carvestrene dihydrochloride and dihydrobromide with HCl and HBr (*Aschan*, Ann. **461**, 1; *Wagner-Jauregg*, ib. **488**, 176).

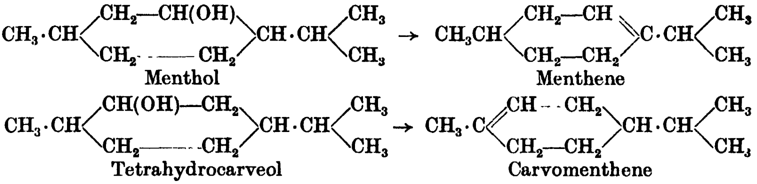
(e) **HYDROTERPENES.** — The terpenes which have just been described are closely related to hydrocarbons containing two more hydrogen atoms in the molecule, which can be obtained from menthol and tetrahydrocarveol (p. 216 and 218), two secondary cyclic alcohols derived from hexahydro-p-cymene, by loss of water: these hydrocarbons are menthene and carvomenthene. Hexahydrocymenes containing four H-atoms more than the terpenes also belong to the hydroterpenes.

Carvomenthene, Δ^1-*p-menthene*, $C_{10}H_{18}$ (formula p. 215), b.p. 175°. Its formation from limonene or terpinene monohydrochloride by reduction with Na + EtOH (p. 208), from α-phellandrene with Na and amyl alcohol (p. 212), and from limonene or dipentene by partial hydrogenation (p. 208) has already been mentioned. The products are more or less optically active, depending on the method of preparation. *Nitrosochloride*, bimolecular, m.p. 87° (*Semmler*, Ber. **40**, 2961); *nitrolbenzylamine*, m.p. 107° (*Vavon*, Bull. **15** (1914), 282). Oxidative degradation, see *v. Braun*, Ber. **62**, 1057. SeO_2 oxidises carvomenthene to carvotanacetone (*Tabuteau*, C. r. **200**, 244).

Menthene, *menthomenthene*, Δ^3-*p-menthene*, $C_{10}H_{18}$, formula below, b.p. 167°, d_4^{20} 0·8129, n_D^{20} 1·45397, can be prepared from menthyl chloride with potassium phenate or from methyl menthyl-xanthate $C_{10}H_{19}OCSSMe$ (*Masson*, Ber. **29**, 1843; *Tchugaeff*, Ber. **32**, 3332; **35**, 2481). It can be prepared from menthol by a large variety of dehydrating agents: heating with dilute sulphuric acid, or with oxalic acid, or with $KHSO_4$, or B_2O_3, or passing menthol vapours over a heated dehydrating catalyst (*Senderens*, Ann. chim. (9) **18**, 117; *Hara*, Mem. Kyoto **9**, 405). Other methods of formation which should be mentioned are: the interaction of neomenthol with thionyl chloride (*Zeitschel*, Ber. **59**, 2298) and the decomposition of the pyrazoline from carvenone hydrazone (*Mereshkovski*, Bull. **37** (1925), 1174). The different preparations are dextro- or laevorotatory in various degrees, depending on the starting materials and the method of preparation.

***d,l*-Menthene** has been prepared by elimination of water from the condensation product of 1,4-methyl-cyclohexanone with isopropyl-magnesium iodide (*Perkin*, J. **89**, 839). *Nitrosochlorides*, bimolecular, see *Baeyer*, Ber. **29**, 11; *Auwers*, ib. **42**, 4905 footnote; *Tchugaev*, C. 1904 I 1347.

The constitution of the two hydrocarbons follows from their relation to carvacrol and menthol. Carvacrol (vol. III) is easily obtained from a rearrangement of carvone (constitution see p. 237) which on reduction yields tetrahydrocarveol (p. 218), an isomer of menthol. The constitution of menthol, on the other hand, is proved by conversion of the corresponding ketone, menthone, into 3-chloro-cymene and thymol. By removing water from these alcohols, or hydrogen chloride from their chlorides, two different tetrahydro-cymenes are formed:



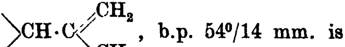
$$CH_3\cdot CH\left<\begin{matrix}CH_2-CH(OH)\\CH_2-CH_2\end{matrix}\right>CH\cdot CH\left<\begin{matrix}CH_3\\CH_3\end{matrix}\right. \rightarrow CH_3CH\left<\begin{matrix}CH_2-CH\\CH_2-CH_2\end{matrix}\right>C\cdot CH\left<\begin{matrix}CH_3\\CH_3\end{matrix}\right.$$

Menthol Menthene

$$CH_3\cdot CH\left<\begin{matrix}CH(OH)-CH_2\\CH_2-CH_2\end{matrix}\right>CH\cdot CH\left<\begin{matrix}CH_3\\CH_3\end{matrix}\right. \rightarrow CH_3\cdot C\left<\begin{matrix}CH-CH_2\\CH_2-CH_2\end{matrix}\right>CH\cdot CH\left<\begin{matrix}CH_3\\CH_3\end{matrix}\right.$$

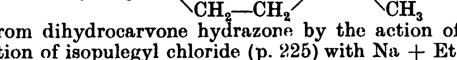
Tetrahydrocarveol Carvomenthene

When oxidised with potassium permanganate, *menthene* yields (1) menthene glycol (p. 221), (2) a keto-alcohol b.p. 105°/13·5 mm, and (3) the fatty acids which are also obtained from menthone (*Wagner*, B. **27**, 1636); *carvomenthene* yields (1) a ketone aldehyde $C_{10}H_{18}O_2$, b.p. about 120°/9 mm., (2) a ketonic acid $C_{10}H_{18}O_3$, β-isopropyl-δ-acetyl-n-valeric acid, b.p. about 175°/9 mm., and (3) β-isopropyl-glutaric acid (*Semmler*, Ber. **40**, 2959).

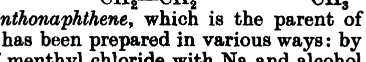
$\Delta^{4(8)}$-Menthene, *dihydro-terpinolene* 

$CH_3\cdot CH\left<\begin{matrix}CH_2-CH_2\\CH_2-CH_2\end{matrix}\right>C:C\left<\begin{matrix}CH_3\\CH_3\end{matrix}\right.$,

b.p. 173°, d^{21} 0·831, has been obtained by decomposing pulegone hydrazone by means of NaOEt (*Semmler*, Ber. **47**, 387), and also from the condensation product of 1,4-methyl-cyclohexanone with bromo-isobutyric ester and zinc by loss of water, and distillation of the resulting unsaturated acid. *Nitrosochloride*, m.p. 102°. On boiling with dilute H_2SO_4 it rearranges into *d, l*-menthomenthene (see above). In the same way the corresponding menthenes of the o- and m-series have been obtained (*Wallach*, Ann. **360**, 70, 75).

$\Delta^{8(9)}$-Menthene, 

$CH_3\cdot CH\left<\begin{matrix}CH_2-CH_2\\CH_2-CH_2\end{matrix}\right>CH\cdot C\left<\begin{matrix}CH_2\\CH_3\end{matrix}\right.$, b.p. 54°/14 mm. is formed from dihydrocarvone hydrazone by the action of NaOEt, and also by reduction of isopulegyl chloride (p. 225) with Na + EtOH. On oxidation it gives hexahydro-p-acetyltoluene and hexahydro-p-toluic acid (*Semmler*, Ber. **39**, 2582; **47**, 384).

The saturated hydrocarbon, $C_{10}H_{20}$, 

$CH_3\cdot CH\left<\begin{matrix}CH_2-CH_2\\CH_2-CH_2\end{matrix}\right>CH\cdot CH\left<\begin{matrix}CH_3\\CH_3\end{matrix}\right.$,

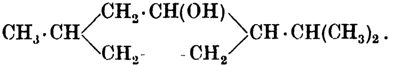
hexahydro-p-cymene, p-menthane, *menthonaphthene*, which is the parent of the p-menthadienes and p-menthenes, has been prepared in various ways: by reduction of menthol with HI, or of menthyl chloride with Na and alcohol (*Jungner*, Ber. **29**, 317; *Kondakov*, J. pr. **60**, 258), by reduction of terpin hydrate (*Schtschukarev*, Ber. **23**, R. 433), of terpineol (*Haller*, C. r. **140**, 1298) and of *d*-limonene (*Smirnov*, C. 1910 I 740), and by the distillation of colophony (*Armstrong*, Ber. **12**, 1761); it is consequently present in resin spirit (p. 90). All these preparations, as well as those obtained in the catalytic hydrogenation of limonene, dipentene, menthene (*Vavon*, C. r. **158**, 409; *Zelinsky*, Ber. **57**, 1070, 2058; Ann. **476**, 60), are not uniform, but mixtures of geometrical isomers. If, on the other hand, p-cymene is hydrogenated under pressure with colloidal Pd as catalyst (*Skita*, Ber. **55**, 148), the product is *cis p-menthane*, b.p. 168·5°, d_4^{20} 0·816, n_D^{20} 1·45149, while catalytic hydrogenation with Ni gives *trans p-menthane*, b.p. 161°, d_4^{20} 0·792, n_D^{20} 1·43931 (*Richter*, Ber. **64**, 876).

m-Menthane, b.p. 167–168° has been obtained from sylvestrene and from m-cymene by catalytic reduction (p. 91). **o-Menthane,** b.p. 171°. For the synthesis of the three cymenes and their reduction to the three menthanes see *Sabatier*, C. r. **156**, 184.

2. ALCOHOLS OF THE MONOCYCLIC TERPENE OR MENTHANE GROUP

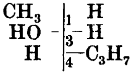
I(a). MONOHYDRIC ALCOHOLS OF MENTHANE. — Hexahydro-p-cymene, p-menthane, can give rise to two secondary alcohols, **Menthol** and **tetrahydrocarveol**, which are position isomers, and three tertiary alcohols, also position isomers, which are known as "tertiary menthols". No primary menthols are known up to the present.

Secondary menthols. — **Menthol,** *menthacamphor*, *5-methyl-2-isopropylhexahydrophenol*

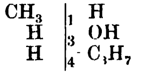


$$CH_3\cdot CH\begin{matrix} \diagup CH_2\cdot CH(OH)\diagdown \\ \\ \diagdown CH_2 - \;\; - CH_2 \diagup \end{matrix}CH\cdot CH(CH_3)_2.$$

There are four possible racemic forms (cf. figure), each of which can be resolved into two optically active forms; two can be converted into menthone, and the two others into isomenthone (*Zeitschel*, Ber. **59**, 2298; *Read*, J. **1934**, 1779)

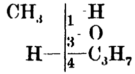


1. Menthol, *l*- *d*-, and *d*, *l*-form

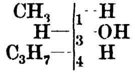


2. Neomenthol, *d*-, *l*- and *d*, *l*-form

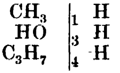
both oxidised to



5. Menthone, *l*-, *d*- and *d*, *l*-form

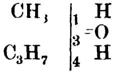


3. Isomenthol, *d*-,*l*- and *d*, *l*-form



4. Neoisomenthol, *d*-, *l*- and *d*, *l*-form

both oxidised to

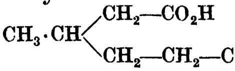
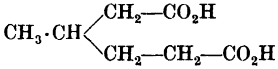


6. Isomenthone, *d*-, *l*-, and *d*, *l*-form

The vertical lines represent the plane of the hexane ring, and the three points of intersection with the horizontal lines are the three carbon atoms 1, 3, 4, which carry the substituents.

Menthol has the configuration (1), with CH_3 trans to C_3H_7 and OH trans to C_3H_7. *Laevo-form* m.p. 43°, b.p. 216°, $[\alpha]_D$ — 49,04° (in 52·37% alcohol); *phenylurethane*, m.p. 112°; *hydrogen phthalate*, m.p. 110° unstable and 120–121° stable. It is the chief constituent of peppermint oil from *Mentha piperita* (Europe, United States) and *Mentha arvensis* var. *piperascens* (Japan). It is obtained, together with *d*-neomenthol, by reducing *l*-menthone (p. 230) into which it is reconverted by CrO_3. The *dextro-form* does not occur in nature, but has been obtained by resolving the racemic form (*Pickard*, J. **101**, 109; *Neuberg*, Fermentforsch. **10** (1929), 491; *Read*, J. **1931**, 188; Brit. Pat. 397,212; *Read*, J. **1934**, 1775) and from *d*-menthone and *l*-isomenthone (*Zeitschel*, J. pr. **133**, 368). **d,l-Menthol,** m.p. 35·5–36·5°, *phenylurethane* m.p. 104°, *hydrogen phthalate* m.p. 132° (Swiss P. 126,585). Methods of preparation are given below. Catalytic dehydrogenation gives menthone, menthene or thymol, depending on the conditions; dehydration yields menthene (p. 214), and catalytic dehydration menthene and menthane at 230°, while at

350° some methyl-cyclopentane is formed (*Hara*, Mem. Kyoto **9** (1926), 405; *Inoue*, Bull. Japan **9**, 353; *Cusmano*, Lincei (6) **4**, 385).

By oxidation with $KMnO_4$ menthol is converted into *oxomenthylic acid*  $CH_3\cdot CH\left\langle\begin{array}{l}CH_2-CO_2H\\ CH_2-CH_2-CO\cdot CH(CH_3)_2\end{array}\right.$, b.p. 174°/15 mm. (*Beckmann*, Ann. **289**, 362) and *β*-methyladipic acid  $CH_3\cdot CH\left\langle\begin{array}{l}CH_2-CO_2H\\ CH_2-CH_2-CO_2H\end{array}\right.$, m.p. 89° (*Manasse*, Ber. **27**, 1818).

Menthyl chloride $C_{10}H_{19}Cl$, b.p. 204°. *Ethyl ether*, b.p. 212°. *Benzoate*, m.p. 54°. *Methyl menthyl-xanthate*, m.p. 39°, gives menthene on dry distillation (*Tchugaev*, Ber. **35**, 2473). The *isovalerate*, b.p. 126°/10 mm., when mixed with 30% free menthol, is used under the name "*validol*" as a sedative. *Chloromethyl-menthyl ether*, $C_{10}H_{19}OCH_2Cl$, b.p. 161°/16 mm., obtained by the action of HCl upon a mixture of menthol and CH_2O (*Wedekind*, Ber. **34**, 813), is used as an antiseptic under the name "*forman*". Menthyl ethoxyacetate ("*coryfin*") and the citrate ("*nasol*", containing glycerol) are used as remedies for colds. — *l*-Menthol is often used for resolving *d,l*-acids, cf. *Abbot*, Ber. **70**, 456.

Neomenthol, configuration (2), b.p. 212°/760 mm, *d*- and *l*-form both liquids, $[\alpha]_D \pm 20{\cdot}7^0$ (*Read*, J. **1934**, 1779) has a disagreeable, pungent odour (*Zeitschel*, J. pr. **133**, 367; *Read*, J. **1933**, 167); *phenylurethane*, m.p. 108°. **d, l-Neomenthol,** m.p. 51°, *phenylurethane* m.p. 114°, *hydrogen phthalate* m.p. 177°. Japanese peppermint oil contains a small percentage of the *d*-form. Neomenthol is formed together with menthol when menthone is reduced or hydrogenated, and is reconverted into menthone by oxidation. It loses water more readily than menthol, to form menthene, which also constitutes the chief product of the action of PCl_5 and of $SOCl_2$. For its separation from menthol by esterification see *Read*, J. **1934**, 1779.

Isomenthol, configuration (3), b.p. 218°, m.p. active 81·5°, *d,l*-form 53·5°; $[\alpha]_D \pm 27^0$ (in alcohol); *hydrogen phthalate*, m.p. active 107·5–108·5°, *d, l*-form 107–108°, can be prepared from piperitone through the steps, isomenthone, isomenthone oxime and isomenthylamine (*Read*, J. **1927**, 1276; **1933**, 170; **1934**, 1779). Isomenthone can be regenerated from it by careful oxidation with CrO_3 (p. 232).

Neo-isomenthol, configuration (4), b.p. 214·5°/760 mm., m.p. (*d, l*-form) 12–14°, *hydrogen phthalate* m.p. 90–92°, is obtained, together with the racemic forms of the other isomers, by catalytic hydrogenation of thymol (*Seel*, C. 1928 I 376; Swiss P. 141,787). Active form see p. 232.

The natural *l*-menthol m.p. 43° has valuable properties as an ingredient of medicines and cosmetics: it is a disinfectant, it has a refreshing taste and stimulates the excretion of bile. It has been found that of the isomers only the corresponding racemic substance has the same valuable properties (*Flury*, C. 1927 I 655; *Seel*, C. 1928 I 376; *Schimmel*, Report **1928**, 114). Hence a number of processes have been worked out for the preparation of synthetic menthol, some of which give the racemic compound, and others a product which is slightly optically active. A few methods may be mentioned here:

(1) *Thymol* is prepared by various methods from cymene or m-cresol, and then hydrogenated with Ni under pressure (G.P. 432,802, 448,950, 453,428, 489,819, 508,893; B.P. 189,450, 213,991, 231,827, 238,314, 239,527, 270,283, 288,122, 297,019, 298,600, 325,856, 326,215; F.P. 627,694; Swiss P. 139,068,

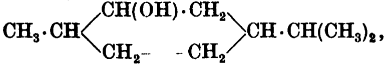
139,804; US.P. 1,768,257, 1,769,648, 1,776,087/8). In addition to *d*, *l*-menthol, liquid mixtures of its isomers are obtained, from which the former is isolated by fractional distillation and crystallisation; Swiss P. 126,585 makes use of the hydrogen phthalate. The isomers can be oxidised to a mixture of menthone and isomenthone which can be again subjected to hydrogenation. Another way of utilising the isomers and converting them into menthol consists in catalytic rearrangement, also with isomenthone and menthone as intermediate steps (B.P. 334,474; US.P. 1,773,500). The hydrogenation of sodium thymate gives a much smaller yield of the isomers (US.P. 1,857,880).

(2) *Piperitone* (p. 233), which is available in quantity in eucalyptus oil from *Eucalyptus dives* and other species, is reduced to menthol either by catalytical hydrogenation, with isomenthone as an intermediate product (*Read*, J. **1927**, 1276; B.P. 213,991, 238,314), or with Na + EtOH. The isomers which are formed together with menthol are transformed into the latter as described in the preceding paragraph.

(3) *Pulegone* (p. 235) yields a slightly active menthone m.p. 34° (*Simmich*, C. 1927 II 2747).

(4) *p-Menthanol-8* (see below) is easily available by catalytic hydrogenation of α-terpineol. It is first transformed into Δ^3-menthene, and this into menthene oxide, either with perbenzoic acid or by adding to it HOCl and removing HCl from the adduct; then menthene oxide is caused to rearrange into menthone, which is reduced as in (1) (*Kötz*, J. pr. **119**, 1; G.P. 455,590, 489,816, 493,268, 493,482).

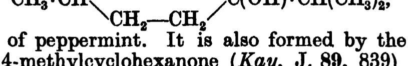
(5) *Citronellal* is converted into isopulegol and this into menthol (*Komatsu*, Mem. Kyoto **11** (1928), 163).



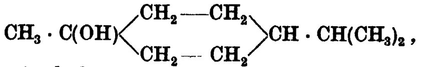
Tetrahydrocarveol, $\mathrm{CH_3\cdot CH}\left\langle\begin{matrix}\mathrm{CH(OH)\cdot CH_2}\\ \mathrm{CH_2 - CH_2}\end{matrix}\right\rangle\mathrm{CH\cdot CH(CH_3)_2}$, like menthol, is known in four isomeric forms: *carvomenthol* and *neocarvomenthol*, and *isocarvomenthol* and *neoisocarvomenthol*. Mixtures of varying composition are obtained from tetrahydrocarvone, carvenone (p. 234) or carvotanacetone (p. 234) by reduction in moist ether; also from nitro-α-phellandrene with Na + EtOH (p. 212) (*Paolino*, Lincei **30**, 265, 313, 371), and from carvenone with Pd and H_2 (*Wallach*, Ann. **414**, 195, 201).

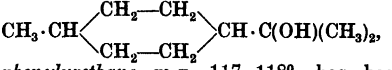
d-Carvomenthol, b.p. 101·8–102°/14 mm.; d_4^{13} 0·9056; $[\alpha]_D$ + 25·08° can be obtained (1) from *d*-carvomenthylamine hydrochloride with $NaNO_2$; (2) from *d*-dihydrocarveol with H_2 and Pd in hydrochloric acid solution; (3) together with *l*-neoisocarvomenthol by hydrogenating a methyl-alcoholic solution of *d*-cis-carveol by means of H_2 and Pd precipitated on $CaCO_3$; (4) together with *l*-neocarvomenthol by reducing *l*-carvomenthone with Al-isopropoxide (*Johnston, Read*, J. **1935**, 1138). When carvacrol is reduced with Ni and H_2, a mixture of racemic carvomenthols is obtained (*Brunel*, C. r. **145**, 1427), which has been resolved by means of the strychnine salts of the carvomenthyl-hydrogen phthalates into four optically active components; these are two pairs of antimers (*Paolino*, Gazz. **55**, 818). The constitution of carvomenthol follows from its relationship to carvacrol (vol. III).

Tertiary menthols are obtained from their iodides, the addition products of menthene or carvomenthene (see above) and HI, with moist silver oxide (*Masson*, Ber. **29**, 1844; *Stephan*, J. pr. **60**, 259). It is a remarkable fact that the addition of hydrogen halides to menthene gives the same tertiary menthyl halides as are obtained by the action of the halides of phosphorus or the hydrogen halides on menthol or tetrahydrocarveol; secondary halides are only byproducts in the latter reaction (*Kurssanov*, C. 1923 III 757).

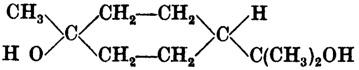


Tertiary menthol-4, $\mathrm{CH_3\cdot CH}\left\langle\begin{matrix}\mathrm{CH_2—CH_2}\\ \mathrm{CH_2—CH_2}\end{matrix}\right\rangle\mathrm{C(OH)\cdot CH(CH_3)_2}$, b.p. 100°/20 mm., smells feebly of peppermint. It is also formed by the action of isopropyl-MgI upon 1,4-methylcyclohexanone (*Kay*, J. **89**, 839) and yields $\Delta^{4(8)}$-menthene (p. 215) on heating with $KHSO_4$.

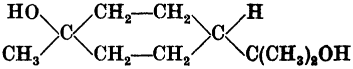
Tertiary menthol-1,  b.p. 101–102°/22 mm., is obtained from β-terpineol by reduction with Pd and H_2 (*Wallach,* Ann. **381,** 58), and, by enlargement of the ring, from dihydrofencholene amine with HNO_2, and from the tertiary chloride obtained from dihydrofencholene alcohol and PCl_5 (*Maxwell,* Ann. chim. (9) **17,** 332). *Phenylurethane* m.p. 100–101°.

Tertiary menthol-8, p-*menthanol-8, dihydro-α-terpineol* (p. 224)  m.p. 35°, b.p. 209°/750 mm., *phenylurethane* m.p. 117–118°, has been synthesised from hexahydro-p-toluic ester and MeMgI (*Perkin,* J. **87,** 639). It occurs in American pine oil. together with α-terpineol, borneol and fenchyl alcohol (*Zeitschel,* Ber. **60,** 1372). (American pine oil is a wood turpentine oil boiling above 200°, and is the starting material in the manufacture of terpineol.) From the hydrogenation product of α-terpineol both the solid trans form and the liquid cis form b.p. 210° of dihydro-α-terpineol have been isolated. *Phenylurethane* of the latter: m.p. 90–92°. It is remarkable that the cis form has a disagreeable musty smell, while the trans form has a scent of flowers, like terpineol itself.

I (b). DIHYDRIC ALCOHOLS. — This group includes the two terpins, *cis terpin* and *trans terpin,* corresponding to the cis and trans dipentene dihydrohalides, with which they are intimately related. The following formulae are assigned to them (*Baeyer,* Ber. **29,** 5; *Ginsberg,* C. 1897 II 420):



cis-Terpin



trans-Terpin.

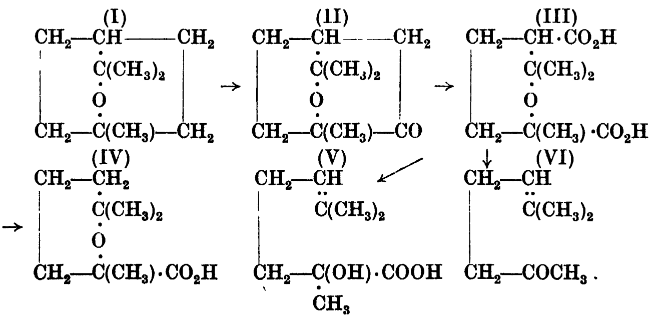
These are in agreement with the oxidation of terpin hydrate to terebic acid (p. 254), as well as with its formation from linalool (p. 202). Cineole (see below) must be regarded as the internal ether of cis-terpin.

Terpin, *1,8-terpin, cis-terpin,* $C_{10}H_{18}(OH)_2$, m.p. 105°, b.p. 258°, readily absorbs water and is converted into a compound distinguished by its great ease of crystallisation, **terpin hydrate,** $C_{10}H_{18}(OH)_2 + H_2O$, m.p. 117° on rapid heating with loss of water, which sublimes at 100° and reverts to terpin when heated at 100° for some time. Terpin corresponds to cis dipentene dihydrobromide (p. 209), from which it can be obtained by treatment with dilute potash, or silver acetate in AcOH, followed by hydrolysis of the resulting diacetyl derivative with alcoholic potash. Terpin hydrate is also formed if turpentine oil is allowed to stand with dilute nitric acid and alcohol (*Wallach,* Ann. **227,** 284), and also from dipentene and *d*-limonene with dilute acids. Terpin is probably an intermediate product in the rearrangement of α- and β-pinene into dipentene which takes place in the presence of acids; it is stable to acids at low temperature, but loses H_2O when heated (*Aschan,* C. 1919 I 284). Terpin is also formed when dipentene or *d*-limonene dihydrochloride are shaken with water, from α-terpineol (p. 223) and cineole (see below), and finally from linalool and geraniol (pp. 201, 202) with dilute acids. It has been obtained synthetically by the action of MeMgI on 1,4-cyclohexanone-carboxylic ester (*Kay,* J. **91,** 372).

Aqueous hydrogen halides convert terpin hydrate into the cis and trans dihydrohalides of dipentene. When boiled with dilute acids it passes into terpineols (*Baeyer,* Ber. **27,** 443, 815), cineole, dipentene, terpinene, and terpinolene (*Robert,* Bull. Pin **1927,** 153). — Terpin hydrate is an ingredient of various medicinal preparations, see e.g. *Burkat,* C. 1935 I 3445.

trans-Terpin, $C_{10}H_{18}(OH)_2$, m.p. 156–158°, b.p. 263–265°, is formed from trans dipentene dihydrobromide (see cis terpin), into which it is completely reconverted on treatment with HBr. It does not combine with water of crystallisation.

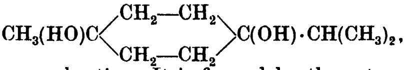
Cineole, *1,8-cineole, eucalyptole* (I) $C_{10}H_{18}O$, m.p. 1–1·5°, b.p. 176°, d^{16} 0·929, n_D 1·4559, a liquid with an odour like that of camphor, is the glycol anhydride corresponding to cis-terpin. It occurs in many essential oils: in *oleum cinae*, the wormseed oil from *Artemisia cina*, in cajuput oil, eucalyptus oils, rosemary oil, sage oil, etc. It is separated from these essential oils by means of concentrated aqueous resorcinol, with which it forms an addition compound decomposed by alkali. Similar compounds are formed with phenol, thymol, and pyrocatechol (*Belucci*, Gazz. **43** II 712) and with certain other phenols (*Morgan*, J. Chem. Ind. **54**, 22). A yellowish green compound with iodole (vol. IV), m.p. 112°, is useful for identification. Furthermore, addition compounds of cineole with HCl, HBr (m.p. 56°), HI + I_2 (*Fromm*, Ann. **405**, 175, 181), phosphoric, arsenic, ferrocyanic, ferricyanic acids (*Baeyer*, Ber. **34**, 2689; *Pickard*, J. **91**, 896), zinc chloride (*Meerwein*, Ann. **455**, 227), and BF_3 (id. J. pr. **141**, 123) are known. With hydrogen halides in AcOH cineole forms dipentene dihydrohalides; with HBr at a low temperature cis-dipentene dihydrobromide (p. 209) is formed. With acetic anhydride in the presence of H_2SO_4 or $FeCl_3$ as catalyst, cineole breaks down into *terpin diacetate* $C_{10}H_{18}(OAc)_2$, b.p. 145°/14 mm., and *terpinyl acetate* $C_{10}H_{17}OAc$ b.p. 104–106°/11 mm. (*Knoevenagel*, Ann. **402**, 111). Cineole is converted into cymene by the action of P_2S_5 and by distillation with zinc dust. Loss of HCl from α-terpineol nitrosochloride (p. 223) under carefully regulated conditions gives *ketocineole oxime* m.p. *d,l* 140° and act. 168°, which can be converted into *ketocineole* (II) m.p. *d,l* 42°, act. 50°; this, when heated with animal carbon and Pd to 230–250°, yields carvacrol quantitatively. Na + EtOH reduce ketocineole to **hydroxycineole,** $C_{10}H_{18}O_2$, m.p. 108°, *phenylurethane* 86·5°, which can be oxidised back to ketocineole by Cr_2O_3 (*Ishidate*, J. Pharm. Japan **48**, 9). When ketocineole is oxidised in acid solution, homoterpenyl-methyl ketone is formed (p. 223), while in alkaline solution the product is *cineolic acid* (III). This ketocineole differs from camphor (p. 282) only in the one O-atom inserted in the bridge and its reactions are somewhat similar to those of camphor; for example it can be converted, first into an isonitroso compound and then into *diketocineole*, which is oxidised by $KMnO_4$ to cineolic acid (III). Diketocineole can be broken down to hydroxy-buchucamphor (hydroxy-diosphenol, see p. 237), and may be converted into dihydro-pinolone by a rearrangement of the ring (*Cusmano*, Gazz. **49** I 26; **53**, 195; **55**, 140; Lincei **27** II 201; *d'Ambrosio*, Gazz. **57**, 717; but cf. *Gandini*, ib. **64**, 594). Potassium permanganate oxidises cineole (I) to cineolic acid (III). The latter is converted, by heating to 160–165° with water, mainly into *cinenic acid* (IV) and by boiling with 30% sulphuric acid into *1,5-dimethyl-1-hydroxyheptene-4-carboxylic-1 acid* (V) (*Rupe*, Helv. **17**, 98); distillation of its anhydride gives methylheptenone (VI) (p. 203):



Cineolic acid (III), $C_{10}H_{16}O_5$, m.p. 197° decomp., *anhydride* m.p. 78°, b.p. 157°/13 mm., gives 2,4-dimethyl-benzoic acid when heated with H_2SO_4 (*Rupe*, Ber. **39**. 4083). **Cinenic acid** (IV), $C_9H_{16}O_3$, m.p. 84°, has been synthesised from the hydrate of methylheptenone by addition of HCN and hydrolysis. Concentrated H_2SO_4 converts it into δ-acetyl-α,α-dimethyl-valeric acid with migration of a methyl group (*Rupe*, Ber. **34**, 2191; **39**, 4083; **41**, 1278; Helv. **17**, 98).

As the dipentene dihydrohalides are related to ordinary terpin, so the terpinene dihydrohalides are related to

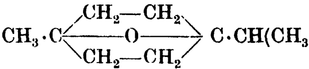
Terpinene-terpin, *1,4-terpin,*



$$\mathrm{CH_3(HO)C}\langle\begin{matrix}\mathrm{CH_2{-}CH_2}\\ \mathrm{CH_2{-}CH_2}\end{matrix}\rangle\mathrm{C(OH)\cdot CH(CH_3)_2},$$

m.p. 138°, b.p. 250°, which sublimes on heating. It is formed by the action of dilute caustic potash on terpinene dihydrochloride, to which it reverts when treated with AcOH + HCl. It is also obtained from sabinene, thujene and the terpinenols with dilute sulphuric acid. Another form, m.p. 116–117°, has been obtained by catalytic hydrogenation of ascaridole with Pd (*Wallach*, Ann. **356**, 200; **392**, 59). Both forms lose water when heated with oxalic acid and give terpinenols and

1,4-Cineole, *terpinene cineole,*



$$\mathrm{CH_3\cdot C}\langle\begin{matrix}\mathrm{CH_2{-}CH_2}\\ \mathrm{{-}O{-}}\\ \mathrm{CH_2{-}CH_2}\end{matrix}\rangle\mathrm{C\cdot CH(CH_3)_2},$$

b.p. 173°, which has been detected in cubeb oil (*Simonsen*, Chem. and Ind. **48**, 92 T). It gives terpinene dihydrobromide with HBr (*Wallach*, Ann. **356**, 204), and the dibasic *1,4-cineolic acid*, m.p. 203° (p. 227) on oxidation with $KMnO_4$ (*Marot*, Bull. Pin **1933**, 30; Germ. Pat. 585,162.—For a dehydro compound see *Butz*, Am. **57**, 1314.

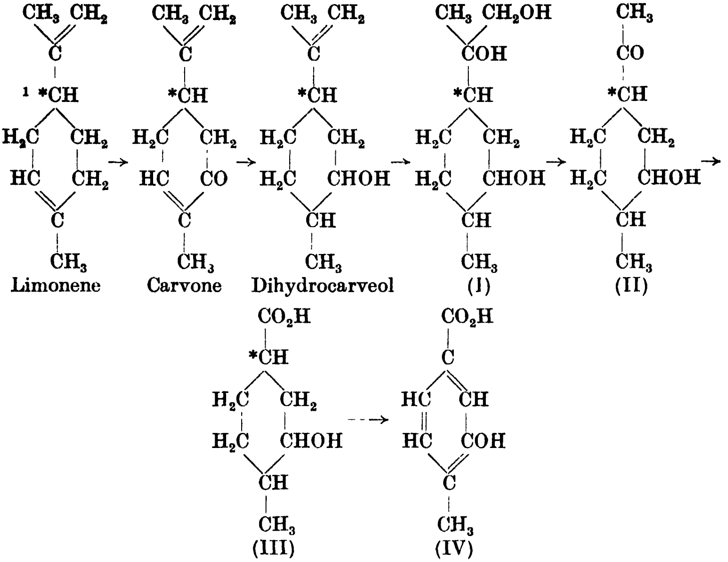
For *sylveterpin*, the meta compound corresponding to terpin, see p. 214 and *Perkin*, J. **91**, 480.

3,4-Menthene glycol, $C_{10}H_{18}[3,4](OH)_2$, m.p. 77° b.p. 130°/13 mm., is obtained by oxidising Δ^3-menthene with $KMnO_4$ (*Wagner*, Ber. **27**, 1636). An isomeric *3,8-menthene glycol* $C_{10}H_{18}[3,8](OH)_2$, m.p. 81°, b.p. 145°/10 mm. is formed, together with isopulegol (p. 225), when citronellal (p. 203) is treated with dilute sulphuric acid; on abstraction of water it is converted into isopulegol (*Barbier*, C. r. **124**, 1308; *Wallach*, Ann. **360**, 103; *Prins*, Chem. Weekbl. **14**, (1917), 627).

p-Menthane-2,8-diol, $C_{10}H_{18}[2,8](OH)_2$, m.ps.: α-form, act. 113°; *d,l* 108–109°; β-form, act., 103°, is formed by reduction of hydroxy-dihydrocarvone, or by shaking dihydrocarveol (p. 225) with dilute H_2SO_4. When boiled with 25% H_2SO_4, it yields an oxide isomeric with cineole, **dihydropinol,** $C_{10}H_{18}O$, b.p. 58°/9 mm, which combines with $K_3Fe(CN)_6$ to a crystalline compound (*Rupe*, Ber. **38**, 1719). A compound stereoisomeric with p-menthane-2,8-diol, **dihydropinol hydrate,** is obtained from pinol hydrate (p. 259) by hydrogenation on Pd, m.p. act. 158–159°, *d, l* 139–141°. It differs from the hydration product of dihydrocarveol by forming terpinene dihydrobromide, m.p. 58°, with HBr in AcOH (*Wallach*, Ann. **414**, 195), a reaction which can only be explained by the assumption that two molecules of H_2O are eliminated with the formation of terpinolene, which then takes up 2 HBr. For **2,4-menthanediols** see *Hamäläinen*, Skand. Arch. Physiol. **27** (1912), 140; *Wallach*, Ann. **414**, 201.

I (c) TRIHYDRIC MENTHANE ALCOHOLS have been obtained by oxidising menthene alcohols with potassium permanganate.

p-Menthane-2,8,9-triol, $C_{10}H_{17}[2,8,9](OH)_3$ (I), from dihydrocarveol (p. 225), is a syrup, and with dilute sulphuric acid yields an unreactive, unsaturated *oxide*, $C_{10}H_{16}O$, b.p. 95°/20 mm. (for its constitution see *Semmler*, Ber. **36**, 765), while oxidation with chromic acid gives a ketonic alcohol, *5-acetyl-hexahydro-o-cresol*, m.p. 58° (II); this is oxidised further to ***hexahydro-m-hydroxy-p-toluic acid***, m.p. 153° (III). The constitution of this last acid follows from its conversion by bromine into ***m-hydroxy-p-toluic acid***, m.p. 203° (IV). These facts are evidence for the following constitutional formulae (*Tiemann*, Ber. **28**, 2141):



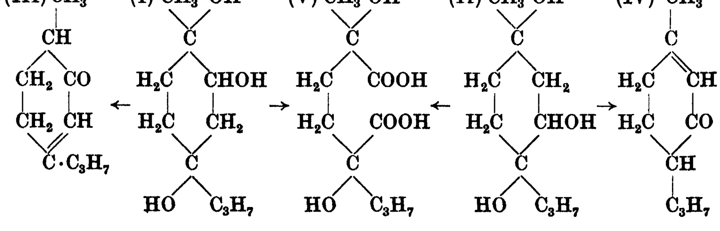
p-Menthane-1,2,8-triol, *dihydroxy-α-terpineol,* $C_{10}H_{17}[1,2,8](OH)_3$, m.p. (*d, l*) 122°, obtained from α-terpineol m.p. 35° (see below) is converted into carvenone (p. 234) by dilute sulphuric acid (*Wallach,* Ann. **277**, 122; *Slavinski,* C. 1918 I 920). Oxidation with CrO_3 gives the ketolactone homoterpenyl methyl ketone (p. 223).

p-Menthane-1,8,9-triol, $C_{10}H_{17}[1,8,9](OH)_3$, m.p. 118°, is obtained from β-terpineol (p. 224).

p-Menthane-1,4,8-triol, $C_{10}H_{17}[1,4,8](OH)_3 + H_2O$, m.p. (anhydrous) 110–112°, b.p. 200°/20 mm., is obtained from $\Delta^{4,8}$-menthenol-1, or γ-terpineol (*Baeyer,* Ber. **28**, 2296; *Henderson,* J. **101**, 2288, 2563).

p-Menthane-1,2,4-triol, $C_{10}H_{17}[1,2,4](OH)_3 + H_2O$ (I), m.p. act. 117°, anh. 129°, and

p-Menthane-1,3,4-triol, $C_{10}H_{17}[1,3,4](OH)_3$, (II), m.p. 121°, are obtained by oxidation of terpinenol-4 and terpinenol-1. When heated with HCl, the former gives carvenone (III), and the latter Δ^1-menthenone-3 (IV). Both are oxidised by $KMnO_4$ to α, α′-dihydroxy-α-methyl-α′-isopropyl-adipic acid (V) (*dilactone,* m.p. 72°). These reactions are important for establishing the constitution of the terpinenols (p. 224) and of terpinene-terpin (p. 221) and are shown in the following scheme (*Wallach,* Ann. **356**, 207; **362**, 261):



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* The asterisk indicates the C-atom to which the optical activity is due.

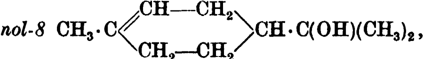
I (d) TETRAHYDRIC MENTHANE ALCOHOLS are formed when certain menthadienes are oxidised with potassium permanganate.

Limonetritol, $C_{10}H_{16}(OH)_4$, m.p. 192°, from *d*-limonene (*Wagner*, Ber. **23**, 2315; *Tiemann*, **28**, 2149); **p-menthane-1,2,4,8-tetrol,** m.p. (anhydrous) 150°, from terpinolene (*Wallach*, Ann. **368**, 10); **p-menthane-1,2,4,5-tetrol,** m.p. 237°, from γ-terpinene, yields a mixture of carvacrol and thymol when heated with dilute H_2SO_4 (*Wallach*, Ann. **362**, 293; *Gildemeister*, C. 1909 II 2159).

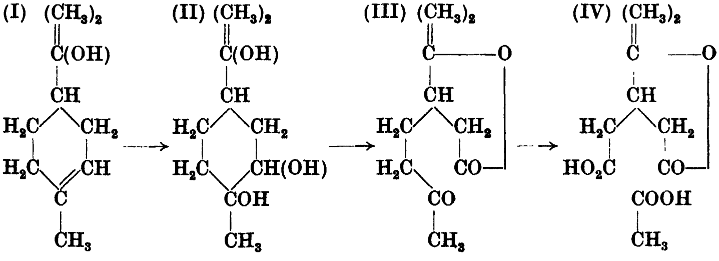
II. MENTHENE ALCOHOLS $C_{10}H_{17}OH$ give trihydric alcohols when oxidised with potassium permanganate (see above).

Terpineols.—The commercial "*liquid terpineol*" used in perfumery is obtained from terpin hydrate (p. 219) by removal of $2H_2O$ with dilute mineral acids or aromatic sulphonic acids. It mainly consists of the two isomeric α- and β-terpineols, m.ps. 35° and 32° (*Wallach*, Ann. **362**, 269).

α-Terpineol, *Δ¹-menthenol-8*

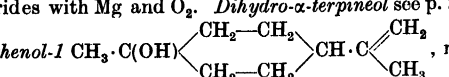


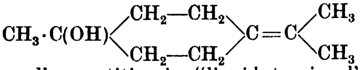
$CH_3\cdot C\left\langle\begin{matrix}CH-CH_2\\CH_2-CH_2\end{matrix}\right\rangle CH\cdot C(OH)(CH_3)_2$, m.p. *d,l* 35°, active 37–38°, b.p. 219°, d^{15} 0·939. For the optical resolution of *d,l*-α-terpineol see *Windaus*, Z. physiol. Ch. **126**, 299, 308; *Fuller*, J. **125**, 2304; *Paolini*, Gazz. **55**, 804. α-Terpineol can also be obtained from limonene monohydrohalides (*Semmler*, Ber. **28**, 2189; *Wallach*, Ann. **350**, 154), from linalool (*Wagner-Jauregg*, Ann. **496**, 52) and geraniol (pp. 201, 202). It has been synthesised by the action of MeMgI upon (1) Δ^1-tetrahydro-p-toluic ester (*Fisher*, J. **93**, 1871); (2) nopinone, the bridge being broken in the reaction (*Wallach*, Ann. **360**, 88); (3) Δ^1-tetrahydro-p-acetyltoluene (p. 125) obtained from β-terpineol (*Wallach*, Ann. **414**, 206). It has a strong smell of lilac. α-Terpineol has been detected in quite a large number of essential oils, sometimes in its optically active and sometimes in its *d,l*-form. It combines with nitrosyl chloride to a bimolecular *nitrosochloride* $[C_{10}H_{17}(OH)(NOCl)]_2$, m.p. act. 107–108°, *d, l* 113°. By removing HCl from this compound an hydroxy-oxime, **8-hydroxy-carvotanacetone oxime,** m.p. 134°, is obtained, which yields carvacrol and carvone when boiled with dilute acids (*Wallach*, Ann. **291**, 342; **345**, 127; **414**, 259). This shows that in α-terpineol and in carvone the carbon atoms are arranged in the same way. α-Terpineol nitrosochloride and limonene nitrosochloride (p. 208) are structural analogues (*Baeyer*, Ber. **29**, 9). For ketocineole from α-terpineol nitrosochloride see p. 220 and *Wallach*, Ann. **414**, 261. α-Terpineol *phenylurethane* m.p. active 109·5°, *d,l* 113°. α-Terpineol in reconverted into terpin hydrate by shaking with dilute sulphuric acid. Potassium permanganate oxidises α-terpineol (I) to *p-menthane-1,2,8-triol* (p. 222) (II), which is further oxidised by chromic acid to a ketolactone, *homoterpenyl-methyl ketone* $C_{10}H_{16}O_3$ (III), m.p. active 47°, *d,l* 64°. If this is again treated with $KMnO_4$ it breaks down into acetic acid and terpenylic acid (IV) (p. 255) (*Wallach*, Ber. **28**, 1773, 1779). *α-Terpineol ozonide* see *Briner*, Helv. **13**, 1030.



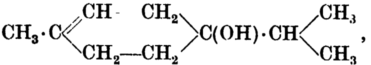
When α-terpineol is heated with $KHSO_4$ it gives *dipentene*, and with oxalic or formic acid *terpinolene* (p. 209) (*Wallach*, Ann. **275**, 104; **368**, 10).

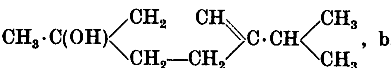
Conversely, limonene or terpinolene can be converted into α-terpineol by treating their hydrochlorides with Mg and O_2. *Dihydro-α-terpineol* see p. 219.

β-Terpineol, *$\Delta^{8(9)}$-menthenol-1*  $CH_3{\cdot}C(OH){<}\begin{matrix}CH_2-CH_2\\ CH_2-CH_2\end{matrix}{>}CH{\cdot}C{<}\begin{matrix}CH_2\\ CH_3\end{matrix}$, m.p. 32°, b.p. 210°, d^{15} 0·923, *nitrosochloride* (bimolecular) m.p. 103° (*Wallach*, Ann. **345**, 127) has not yet been found in essential oils, but is present in commercial terpineol (*Stephan, Helle*, Ber. **35**, 2147). *Phenylurethane* m.p. 85°. Catalytic reduction leads to tertiary menthol-1 (p. 219). Oxidation with $KMnO_4$ gives p-menthane-1,8,9-triol (see above), and further oxidation with chromic acid 4-acetyl-1,1-methyl-cyclohexanol; this can be converted into Δ^3-tetrahydro-p-acetyl-toluene (p. 125), p-acetyl-toluene, and p-toluic acid (*Stephan* and *Helle*, l. c.; *Wallach*, Ann. **324**, 79). For the synthesis of β-terpineol, see *Perkin*, J. **85**, 654. For its conversion into α-terpineol through tetrahydro-p-acetyl-toluene, see *Wallach*, Ann. **414**, 206.

γ-Terpineol, *$\Delta^{4(8)}$-menthenol-1*  $CH_3{\cdot}C(OH){<}\begin{matrix}CH_2-CH_2\\ CH_2-CH_2\end{matrix}{>}C{=}C{<}\begin{matrix}CH_3\\ CH_3\end{matrix}$, m.p. 69°, is apparently present in small quantities in "liquid terpineol" (*Baeyer*, Ber. **27**, 815; *Robert*, Bull. Pin **1927**, 153), and probably also in the oil of *Cupressus torulosa* (*Simonsen*, Ind. For. Rec. **10** (1923), pt. 1). Its acetate is obtained by treating tribromo-menthane or tetrahydro-dipentene tribromide (p. 209) with AcOH and zinc dust. AcOH + HCl convert it into a mixture of dipentene and terpinene dihydrochlorides (*Wallach*, Ann. **350**, 160). It forms a blue *nitrosochloride*, m.p. 82°, with NOCl, like Me_4-ethylene (For the nitrosochloride of γ-terpinyl acetate see *Germuth*, Am. Pharm. **99** [1927], 402.) Consequently, it must also contain a tertiary-tertiary double bond. In addition, its OH group must be in such a position that dipentene dihydrobromide can be produced with HBr.

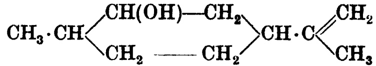
Terpinenols.—Just as ordinary terpin (p. 219) gives unsaturated alcohols by loss of one molecule of water, so terpinene-terpin (p. 221) gives unsaturated alcohols, which are called *terpinenols* (*Wallach*, Ann. **356**, 206; **362**, 261).

Terpinenol-4, *Δ^1-menthenol-4*  $CH_3{\cdot}C{<}\begin{matrix}CH-CH_2\\ CH_2-CH_2\end{matrix}{>}C(OH){\cdot}CH{<}\begin{matrix}CH_3\\ CH_3\end{matrix}$, b.p. 212°, is found as the *d*-form in cardamom and marjoram oils (*Wallach*, Ann. **350**, 168; **356**, 206), and in the *l*-form in the oil of *Eucalyptus dives* (*Schimmel*, Report **1928**, 50). It has also been detected in Spanish thyme oil, nutmeg oil, etc. *d*-Terpinenol-4 is formed by shaking sabinene or thujene with dilute H_2SO_4; sabinene hydrate (p. 241) must be assumed to be the intermediate product, which under these conditions is easily converted into terpinenol-4. *d,l*-Terpinenol-4 is produced by the action of dilute caustic potash upon terpinene dihydrochloride, and from terpinene-terpin with aqueous oxalic acid. With the hydrogen halides in AcOH it yields terpinene dihydrohalides; with dilute H_2SO_4 terpinene-terpin. On oxidation with $KMnO_4$ p-menthane-1,2,4-triol (see above) is formed. *Nitrosochloride*, act., m.p. 115–116°; *phenylurethane*, act., m.p. 71–72°.

Terpinenol-1, *Δ^3-menthenol-1*  $CH_3{\cdot}C(OH){<}\begin{matrix}CH_2\quad CH\\ CH_2-CH_2\end{matrix}{>}C{\cdot}CH{<}\begin{matrix}CH_3\\ CH_3\end{matrix}$, b.p. 209°, is found in the first runnings in the distillation of industrial terpineol, and occasionally in essential oils, e.g. in camphor oil. It has been synthesised from 4-isopropyl-cyclohexene-3-one-1 (p. 116) and MeMgI (*Wallach*, Ann. **362**, 280). On oxidation it yields p-menthane-1,3,4-triol (p. 222). **Menthone-enol,** *Δ^3-menthenol-3* see p. 231.

Carvenol, *Δ^8-menthenol-2*, b.p. 219–221°, is oxidised to carvenone (p. 234), from which, however, it has not yet been obtained by reduction. It has been prepared by the loss of H_2O from p-menthane-2,4-diol (*Wallach*, Ann. **414**, 202).

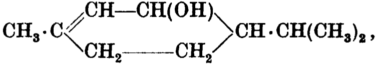
Dihydrocarveol, *Δ⁸⁽⁹⁾-menthenol-2*



$$\mathrm{CH_3\cdot CH}\left\langle\begin{array}{l}\mathrm{CH(OH)-CH_2}\\ \mathrm{CH_2 - CH_2}\end{array}\right\rangle\mathrm{CH\cdot C}\left\langle\begin{array}{l}\mathrm{CH_2}\\ \mathrm{CH_3}\end{array}\right.,$$

b.p. 224°, d^{15} 0·937, n_D 1·48168, is a mixture of stereoisomers and is optically active, with a pleasant smell recalling that of the terpineols; it has been found in caraway oil (*Schimmel*, Report April **1905**, 20) and, as acetate, in American spearmint oil; it is formed in the reduction of carvone (p. 237). Dry distillation of *d*-dihydrocarveol-methyl-xanthate gives *l*-limonene and possibly, *l*-isolimonene (*Tchugaev*, C. 1908 I 1180).

Piperitol, *Δ¹-menthenol-3*,

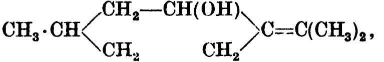


$$\mathrm{CH_3\cdot C}\left\langle\begin{array}{l}\mathrm{CH-CH(OH)}\\ \mathrm{CH_2 - CH_2}\end{array}\right\rangle\mathrm{CH\cdot CH(CH_3)_2},$$

b.p. 95–96°/10 mm, d^{22} 0·923, occurs together with Δ¹-menthenone-3 (*piperitone*) in the oils from several species of the "peppermint group" of the genus *Eucalyptus*. On oxidation it yields piperitone, which can be reduced only in poor yield to piperitol with Al isopropoxide. It can also be obtained from piperitone hydrazone and from *l*-piperityl-trimethylammonium iodide with Ag_2O. In the last reaction a second geometrically isomeric form of piperitol is also formed which spontaneously loses water to give α-phellandrene (*Read*, J. **1930**, 277; **1934**, 308; Chem. & Ind. **49**, 519).

For **carvotanacetol,** *Δ¹-p-menthenol-6*, see p. 235.

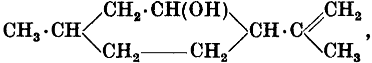
Pulegol, *Δ⁴⁽⁸⁾-menthenol-3*



$$\mathrm{CH_3\cdot CH}\left\langle\begin{array}{l}\mathrm{CH_2-CH(OH)}\\ \mathrm{CH_2 \quad CH_2}\end{array}\right\rangle\mathrm{C{=}C(CH_3)_2},$$

b.p. 91·5°/12 mm, d_4^{18} 0·909°, is formed, in small yield together with menthols (p. 218), when pulegone is reduced with the calculated quantities of Na and EtOH (*Paolino*, Lincei (5) **28** II 190, 236), or in better yield by reducing pulegone with Al isopropoxide (*Doeuvre*, Bull. **2** (1935), 298).

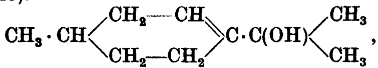
Isopulegol, *Δ⁸⁽⁹⁾-menthenol-3*



$$\mathrm{CH_3\cdot CH}\left\langle\begin{array}{l}\mathrm{CH_2\cdot CH(OH)}\\ \mathrm{CH_2 - CH_2}\end{array}\right\rangle\mathrm{CH\cdot C}\left\langle\begin{array}{l}\mathrm{CH_2}\\ \mathrm{CH_3}\end{array}\right.,$$

b.p. 88°/10 mm, d_4^{18} 0·911, n_D^{18} 1·4716, is obtained by the rearrangement of citronellal under the action of acids (*Doeuvre*, Bull. **53** (1933), 27, 170) (p. 203) and reverts to citronellal when heated (*Grignard*, C. r. **190**, 1164; *Doeuvre*, Bull. **53** (1933), 170, 589). The enol form of citronellal is possibly an intermediate in this reaction. Isopulegol has been found in some essential oils, but always together with citronellal, which seems to be its source in the plant. When heated with NaOEt in an autoclave, isopulegol is partly reduced to citronellol and partly broken down into 1-methyl-cyclohexanone-3 and acetone (*Schimmel*, Report October **1913**, 80); pulegol is presumably the primary product of rearrangement in the decomposition. There are four possible geometrically isomeric forms of isopulegol, as there are of menthol, but only two are known, one *l*-isopulegol (*hydrogen phthalate*, m.p. 106°), which has the same configuration as p-menthol, and one, *d*-α-isopulegol, which yields *d*-neomenthol with Pd and H_2, and therefore corresponds to the latter. Both forms of isopulegol are oxidised to the same isopulegone (p. 236) (*Pickard*, J. **117**, 1248).

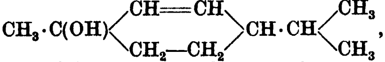
*Δ*³**-Menthenol-8**



$$\mathrm{CH_3\cdot CH}\left\langle\begin{array}{l}\mathrm{CH_2-CH}\\ \mathrm{CH_2-CH_2}\end{array}\right\rangle\mathrm{C\cdot C(OH)}\left\langle\begin{array}{l}\mathrm{CH_3}\\ \mathrm{CH_3}\end{array}\right.,$$

m.p. 39°, b.p. 97°/14 mm, is obtained by the action of MeMgI on Δ³-tetrahydro-p-toluic ester or Δ³-tetrahydro-p-acetyl-toluene (*Perkin*, *Wallach*, J. **97**, 1427).

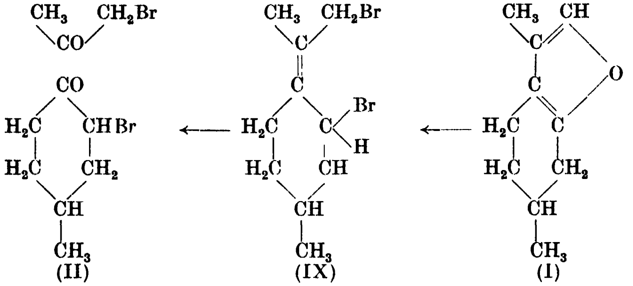
*Δ*²**-Menthenol-1**

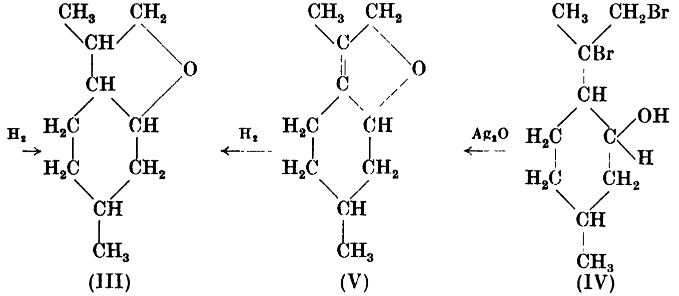


$$\mathrm{CH_3\cdot C(OH)}\left\langle\begin{array}{l}\mathrm{CH{=}CH}\\ \mathrm{CH_2-CH_2}\end{array}\right\rangle\mathrm{CH\cdot CH}\left\langle\begin{array}{l}\mathrm{CH_3}\\ \mathrm{CH_3}\end{array}\right.,$$

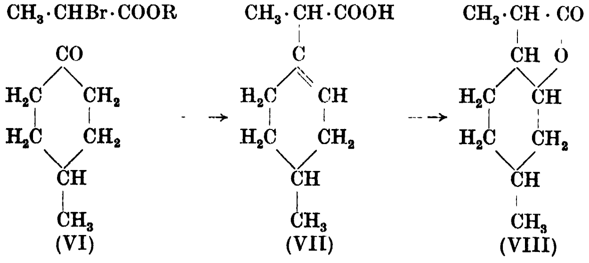
b.p. 92°/10 mm, formed by interaction of 4-isopropyl-cyclohexene-2-one-1 and MeMgI, loses water easily with the formation of α-phellandrene (p. 212) (*Wallach*, Ann. **359**, 283).

Menthofuran, $C_{10}H_{14}O$ (I), m.p. —17°, b.p. 196°, d^{20} 0·963, n_D^{20} 1·48519, $[\alpha]_D$ + 93·4°, has been extracted from the oil of peppermint flowers and plays a large part in the pleasant smell of peppermint. Its solution in glacial acetic acid gives a characteristic blue colour when exposed to the air. Oxidation gives β-methyladipic acid, and reduction p-menthane, with (III) as an intermediate; the ozonisation of its bromo derivative (IX) gives monobromo-acetone and 2-bromo-4-methyl-cyclohexanone (II):

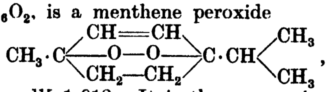




Tetrahydro-menthofuran (III) has been synthesised (1) from the bromo derivative (IV) of isopulegol with Ag_2O by way of the dihydro compound (V); (2) from 4-methyl-cyclohexanone (VI) with bromo-propionic ester by way of the unsaturated acid (VII) and the lactone (VIII) (*Wienhaus*, Z. angew. Ch. **47**, 415).

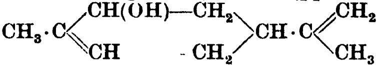


Ascaridole, $C_{10}H_{16}O_2$, is a menthene peroxide

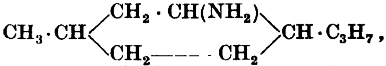


$$CH_3\cdot C\begin{matrix}\diagup CH{=}CH\diagdown \\ {-}O{-}O{-} \\ \diagdown CH_2{-}CH_2\diagup\end{matrix}C\cdot CH\begin{matrix}\diagup CH_3 \\ \diagdown CH_3\end{matrix},$$

b.p. 108–110°/15 mm, d^{15} 1·012. It is the very poisonous active principle of chenopodium or American wormseed oil. When it is heated to 150° a violent reaction takes place resulting in complete rearrangement of the molecule (*Thoms*, C. 1930 I 1796) and the formation of an isomeric compound $C_{10}H_{16}O_2$. This must be **2,3-oxido-1,4-cineole,** since on hydration it yields chiefly *1,4-oxido-p-menthane-2,3-diol* $C_{10}H_{18}O_3$, the constitution of which is proved by its oxidation to *ascaridic acid* = 1,4-cineolic acid (p. 221; *Nelson*, Am. **36**, 2521). As by-products, *1,2,3,4-tetrahydroxy-p-menthane* and *2,3-oxido-p-menthane-1,4-diol* are formed (*Richter*, Ber. **64**, 878). 1,4-Oxido-p-menthane-2,3-diol can be converted into the yellow dihydroxythymoquinone, while catalytic reduction yields one form of 1,4-terpin (m.p. 116–117°) (p. 221; *Wallach*, Ann. **392**, 59).

III. MENTHADIENE ALCOHOLS.—Pulegone-enol and **isopulegone-enol** are discussed in connection with the corresponding ketones (pp. 235, 236). **Carveol,** $\Delta^{6,8(9)}$*-menthadiene-2-ol,*  $\mathrm{CH_3{\cdot}C}\!\left\langle\begin{matrix}\mathrm{CH(OH)—CH_2}\\ \mathrm{CH\qquad -\,CH_2}\end{matrix}\right\rangle\mathrm{CH{\cdot}C}\!\left\langle\begin{matrix}\mathrm{CH_2}\\ \mathrm{CH_3}\end{matrix}\right.$ contains two dissimilar asymmetric carbon atoms, and hence should exist as two stereoisomers, each of which should be resolvable. A *d, l*-carveol, b.p. 226–227°, d^{15} 0·9578, n_D^{18} 1·4961, *phenylurethane*, m.p. 94–95°, is formed in the autoxidation of limonene together with *d,l*-carvone (*Blumann*, Ber. **47**, 2623; *Treibs*, ib. **61**, 459), into which it can be converted by oxidation with CrO_3. Reduction of *d*-carvone with aluminium isopropoxide gives an optically active carveol (*Ponndorf*, Z. angew. Ch. **39**, 138), which can be separated by crystallisation of the 3,5-dinitrobenzoate into *d*-trans-carveol (OH and C_3H_5 on opposite sides of the ring), b.p. 102°/10 mm, and *d*-cis-carveol, m.p. 24–25°, b.p. 101°/10 mm. Similar reactions from *l*-carvone give *l*-trans-carveol and *l*-cis-carveol (*Read*, J. **1934**, 233). Removal of water from carveol gives p-cymene; its hydrogenation leads to carvomenthol (p. 218). **Carveol methyl ether,** $C_{10}H_{15}OMe$, b.p. 208–212°, d^{18} 0·9065, n_D^{18} 1·47586, is obtained from limonene tetrabromide by the action of sodium on its solution in MeOH. It is oxidised by chromic acid to *d,l*-carvone (*Wallach*, Ann. **281**, 140). **Perillyl alcohol** cf. p. 229.

3. BASES OF THE MONOCYCLIC TERPENE OR MENTHANE GROUP

MENTHANE BASES are obtained by reducing the oximes of menthane ketones with sodium and alcohol or by heating the ketones with ammonium formate. All the four **menthylamines** $C_{10}H_{19}NH_2$,  $\mathrm{CH_3{\cdot}CH}\!\left\langle\begin{matrix}\mathrm{CH_2\cdot CH(NH_2)}\\ \mathrm{CH_2———CH_2}\end{matrix}\right\rangle\mathrm{CH{\cdot}C_3H_7}$, corresponding to the four 3-menthanols (cf. diagrams p. 216), are known (*Read*, *Storey*, J. **1927**, 2168; **1930**, 2761; **1934**, 1779).

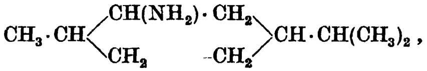
Menthylamine (configuration 1), b.p. 81–82°/12 mm, is produced by reducing optically active menthone oxime with Na + EtOH; its rotation is of the same sign as that of the original material, while a small quantity of isomenthylamine formed simultaneously, has the opposite rotation. *Formyl compound* m.p. active 102°, *d,l* 78°. With nitrous acid menthol is easily formed, the sign of rotation remaining the same. The formyl compound is also obtained together with other products (see below) by the action of ammonium formate on menthone. *Phenylcarbamide*, m.p. active 141°, *d,l* 162°. When the dibromyl compound of *l*-menthylamine is treated with Ag_2O, it gives *menthone l-menthylhydrazone*, $C_{10}H_{19}NH{\cdot}N{:}C_{10}H_{18}$, m.p. 92–93°, which can be hydrolysed to ***l*-menthylhydrazine,** $C_{10}H_{19}NHNH_2$, b.p. 241° (*Kishner*, J. pr. **52**, 424). This compound is a valuable reagent for resolving racemic aldehydes and ketones (*Neuberg*, Ber. **36**, 1192). *l-Menthylisocyanate* $C_{10}H_{19}{\cdot}N{:}CO$, b.p. 110°/12 mm, can be used for resolving racemic alcohols (*Neville*, J. **85**, 685); it has been obtained by treating *l*-menthylamine with chlorocarbonic ester and distilling the resulting menthyl carbamic ester with P_2O_5. Another method of using *l*-menthylamine for the resolution of an active alcohol is to treat the alcohol with chloracetyl chloride: the chloracetate formed reacts with menthylamine to give the ester of menthylglycine, $C_{10}H_{19}NHCH_2CO_2R$ which can be separated by recrystallisation of the compound or of its salts into diastereo-isomers (*Read*, J. **1934**, 1775).

Neomenthylamine (configuration 2, p. 216), b.p. 84°/13 mm, is obtained, as its *formyl derivative*, m.p. act. 118°, *d,l* 86°, from menthone and also from isomenthone, together with formyl menthylamine; *l*-menthone and *d*-isomenthone give the *d*-form (*Wallach*, Ann. **350**, 278). *Phenylcarbamide*, m.p. act. 178°, *d,l* 184°. With nitrous acid the chief product is Δ^3-menthene with a rotation of the same sign as that of the amine. By treating the dibromylamine with Ag_2O, **menthazine** $C_{10}H_{18}{=}N{\cdot}N{=}C_{10}H_{18}$, m.p. act. 51°, has been obtained (*Kishner*, C. 1900 I 654).

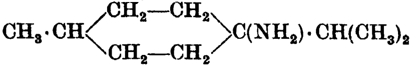
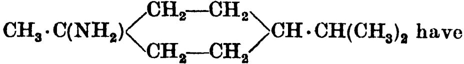
Isomenthylamine (configuration 3, p. 216), b.p. 87°/13,5 mm., has been obtained from isomenthone oxime with Na and EtOH, as in the preparation of menthylamine, and yields isomenthol with HNO_2, all these substances having a rotation of the same sign. *Formyl compound* m.p. act. 45–46°, *d,l* 45–47°; *phenylcarbamide* act. and *d,l* m.p. 142°.

Neoisomenthylamine (configuration 4, p. 216), b.p. 89°/14·5 mm., has been obtained as the *d*-form from the reaction product of ammonium formate and *l*-menthone. *Phenylcarbamide*, m.p. 150°. The principal product of its reaction with nitrous acid is *d*-Δ^3-menthene, as in the case of *d*-neomethylamine, since neomenthol and neoisomenthol, the alcohols first formed, lose water very readily.

Carvomenthylamine, *tetrahydro-carvylamine*, $C_{10}H_{19}NH_2$,



can exist in four forms corresponding to the menthylamines. Reduction of *l*-carvomenthone oxime with Na and alcohol (*Wallach*, Ann. **277**, 137; *Brunel*, C. r. **145**, 1427) gives mainly *d*-carvomenthylamine, b.p. 89·8–90·0°/16·5 mm., $[\alpha]_D^{25}$ + 12·47°, and some *l*-neocarvomenthylamine, b.p. 87·8–88·0°/16 mm., $[\alpha]_D^{25}$ — 26·55°; both compounds are also formed in the interaction of *l*-carvomenthone and ammonium formate (*Read*, J **1934**, 226; *W. Huckel*, Ann. **526**, 115). **l-Isocarvomenthylamine,** m.p. 90°/15 mm., $[\alpha_D^{18}]$ — 14·7°, is obtained similarly from *l*-isocarvomenthone oxime, but neo-iso-carvomenthylamine is still unknown (*Read*, J. **1935**, 1138).

Tert. Menthylamine,  and **tert. Carvomenthylamine,**  have been obtained by the interaction of menthene hydrobromide and carvomenthene hydrobromide with silver cyanate, and subsequent hydrolysis (*Baeyer*, Ber. **26**, 2270, 2562).

2,4-Diamino-menthane, $C_{10}H_{18}(NH_2)_2$, b.p. 121°/12 mm., from carvenone-hydroxylamino-oxime (*Harries*, Ber. **41**, 2528).

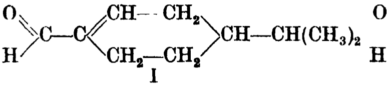
MENTHENE BASES have been prepared by the reduction of the oximes of menthene ketones.

Carvenylamine, $C_{10}H_{17}NH_2$, b.p. 86–89°/10 mm., from carvenone oxime with Al amalgam, forms a hydrochloride which gives α-terpinene on distillaton (*Harries*, Ber. **41**, 2524). **Dihydro-carvylamine,** $C_{10}H_{17}NH_2$, b.p. 219°, d^{20} 0·889, n_D 1·48294, is optically active and is obtained by reducing carvone oxime in alkaline solution. Its hydrochloride decomposes when heated, rearrangement taking place and terpinene and cymene being formed (*Wallach*, Ann. **368**, 13). In the reduction of carvone oxime by AcOH, EtOH and zinc dust, both double bonds are unattacked and **carvylamine** $C_{10}H_{15}NH_2$, b.p. 94–95°/12·5 mm., is formed. *Benzoyl derivative*, m.ps. α 174°, β 110° (*Mailhe*, Bull. **33** (1923), 83; *Morell*, Ann. **410**, 70). **Pulegylamine** (*Beckmann*, Ann. **262**, 13; *Wallach*, Ann. **289**, 337). **Dihydroperillylamine**: *Williams*, C. 1930 I 2086.

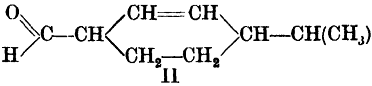
Nitrolamines have been obtained from the nitrosochlorides, e.g. from those of the limonenes, by the action of primary and secondary bases.

4. ALDEHYDES OF THE MONOCYCLIC TERPENE OR MENTHANE GROUP

Phellandral, *Δ^1-tetrahydro-cuminaldehyde* $C_{10}H_{16}O$, b.p. 89°/5 mm., d^{20} 0·9412, n^{20}_D 1·4912, occurs as the *l*-form in the oil of water fennel and of several species of eucalyptus. *Oxime*, active, m.p. 87°; *semicarbazone*, active, m.p. 204°. An aldehyde very similar to phellandral (*semicarbazone* m.p. 201–202°) has been obtained from phellandrene glycol (*Wallach*, Ann. **340**, 15). When oxidised with $KMnO_4$, phellandral gives a dihydric acid $C_9H_{16}O_4$, m.p. 72°, which is thought to be the active β-isopropyladipic acid (id. Ann. **343**, 33). Phellandral is therefore given the formula (I), while (II) was attributed to **cryptal,** b.p. 98–100°/10 mm., d^{20} 0·9442, n^{20}_D 1·4380, the *l*-form of which occurs together with phellandral and cuminaldehyde in the oils of *Eucalyptus hemiphloia, polybractea* and *Bakeri*. Cryptal has, however, been shown to be $C_9H_{14}O$, 4-isopropyl-Δ^2-cyclohexenone (p. 115), since oxidation of the dihydro compound gives β-isopropyladipic acid (*Cahn, Penfold* and *Simonsen*, J. **1931**, 1366; *Berry, Macbeth* and *Swanson*, J. **1937**, 986).

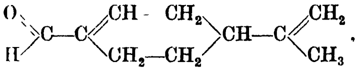


I



II

Perillaldehyde, *$\Delta^{1,8(9)}$-dihydrocuminaldehyde* $C_{10}H_{14}O$,



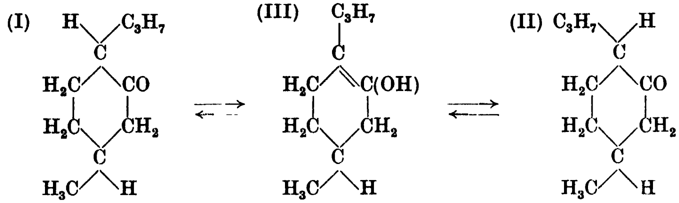
, b.p. 234–236°, occurs as the *l*-form in perilla oil and as the *d*-form in the oil of "false camphor wood" from *Hernandia peltata* (*Semmler*, Ber. **44**, 815). *Semicarbazone*, act. m.p. 200°, *oxime*, act. m.p. 101–102°. CrO_3 produces **perillic acid** m.p. 132°, *dibromide* m.p. 166–167°. The reduction of perillaldehyde with zinc dust and acetic acid gives **perillalcohol** $C_{10}H_{16}O$, b.p. 119–120°/11 mm., in the form of its *acetate*, b.p. 123–126°/13 mm.; *α-naphthylurethane*, m.p. 146–147°. It occurs in nature in the oils of gingergrass, spearmint, etc. Its chloride has been reduced to dipentene by Na + EtOH, which proves its constitution (*Semmler*, Ber. **44**, 460). For syntheses with perillaldehyde, see *Rutovski*, C. 1928 II 2355. **Dihydroperillyl alcohol** see p. 122. It is worth noticing that perillaldehyde and myrtenal (p. 260) occur together in "false camphor wood" oil. These two aldehydes are related in the same way as limonene and α-pinene. From the wood of the American red cedar *Thuja plicata* an acid $C_{10}H_{12}O_2$, m.p. 88°, has been isolated which has been converted into cuminic acid, and for this reason and because of its ozonisation products has been formulated as a *dehydro-perillic acid* (p. 133).

Cyclocitrals see p. 205.

5. CYCLIC KETONES OF THE MONOCYCLIC TERPENE OR MENTHANE GROUP

Ketones belonging to this group are found in plants; they can be prepared by oxidation of the corresponding secondary alcohols, and on further oxidation they give lactones and aliphatic carboxylic acids; the structure of these degradation products provides valuable evidence for the structure of the cyclic ketones and their derivatives. Since these ketones contain asymmetric carbon atoms, they often occur in optically active forms. As with other ketones, the cyclic ketones of the terpene group are identified by means of their oximes and their sparingly soluble semicarbazones.

I. KETOMENTHANES, KETOHEXAHYDRO-p-CYMENES, $C_{10}H_{18}O$.— **p-Menthanone-3** is known in two stereoisomeric forms, *menthone* (I) and *isomenthone* (II), which have the common enolic form, *Δ^3-menthenol-3* (III). Menthone is sterically related to menthol and neomenthol (p. 216), and isomenthone to isomenthol and neoisomenthol (*Zeitschel*, Ber. **59**, 2298). Menthone and isomethone are both known in *d*-, *l*- and *d,l*-forms.



l-**Menthone**, b.p. 210°/760 mm., d^{20} 0·8937, n_D^{20} 1·44952, $[\alpha]_D$ — 28°, occurs in American, Russian and Japanese peppermint oils together with menthol, menthol esters, menthene and limonene. It has been prepared by oxidising *l*-menthol and *d*-neomenthol with potassium bichromate and sulphuric acid at a temperature not exceeding 50° (*Beckmann*, Ann. **250**, 322), and by dehydrogenating *l*-menthol (*Ponndorf*, C. 1926 I 1983; *Hara*, Mem. Kyoto 9 (1926), 405; *Cusmano*, Lincei 4 (1926), 385). *d*-Menthone is seldom found in natural products (*Murayama*, J. Pharm. Soc. Japan **1921** No. 476), but can be obtained by oxidising *l*-neomenthol or *d*-menthol (*Read*, J. **1929**, 23), or by catalytic hydrogenation of *d*-piperitone (id. Ch. & Ind. **46**, 871), a reaction in which *l*-isomenthone is also formed. *Semicarbazone*, m.p. act. 184°, *d,l* (α) 186° and *d,l* (*β*) 161°. *d,l*-Menthone has been obtained by similar methods, and also from menthene (Germ. Pat. 489,819, 493,268, 493,482; French Pat. 723,395) and from pulegone (*Doeuvre*, Bull. **2** (1935), 298). For its industrial production, see menthol and Germ. Pat. 512,719, 514,417. *d,l*-Menthone has been synthesised from *β*-methylpimelic ester by means of an internal acetoacetic ester condensation (p. 19), introduction of the isopropyl group and hydrolysis (*Einhorn*, Ber. **34**, 3793). An optically active menthone is obtained when active 1,3-methyl-cyclohexanone, a decomposition product of pulegone (p. 235), is treated with sodamide and isopropyl iodide (p. 110, and *Haller*, C. r. **140**, 130). For other syntheses of menthone see p. 138, and *Kötz*, Ann. **342**, 306; **357**, 209 and *Sen*, J. Ind. ch. Soc. **5** (1928), 609, and for its formation by the rearrangement of 3-menthene oxide see *Kötz*, J. pr. **119**, 1; French Pat. 723,395.

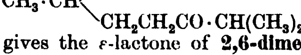
With cold conc. sulphuric acid *l*-menthone rearranges into *d*-isomenthone (see below) (*Beckmann*, Ber. **42**, 846), and the same rearrangement takes place with alkalies or other catalysts, e.g. by heating with Cu (*Komatsu*, Mem. Kyoto **9**, 23); the enolic form (III) is the intermediate stage. The final product is a mixture of menthone and isomenthone in varying proportion, from which menthone can be separated as semicarbazone. A similar mixture is obtained by the catalytic hydrogenation of compounds of the menthenone-3 structure, such as piperitone, pulegone, and Δ^4-menthenone-3. For a method of converting these mixtures into pure menthone see *Read*, J. **127**, 2782.

Δ^3-**p-Menthenol-3** (III), the enolic form of menthone, is obtained as its *acetate*, b.p. 210—212°, (1) from menthone with NaOAc and Ac_2O (*Mannich*, Ber. **41**, 570); (2) from menthone with organomagnesium compounds and acetyl chloride (*Grignard*, Bull. Belg. **36** [1927], 97). The free enol, b.p. 75—77°/2 mm., d_4^{11} 0·893, n_D^{11} 1·45987, smells like menthone and at 8° combines with exactly 1 mol. of bromine. The rearrangement into the keto form begins spontaneously soon after distillation, and is instantaneous in the presence of alkalies or acids.

For "normal menthone", *1-methyl-4-normalpropyl-cyclohexanone-3* see *Wallach*, Ann. **414**, 214.

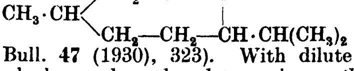
The constitution of menthone (cf. p. 204) is known, not only from its synthesis, but also from the following facts: (1) It can be converted into 3-chlorocymene; when menthone is treated with PCl_5, dichloro-hexahydrocymene is obtained, which gives tetrahydro-chlorocymene by loss of HCl; when this is dehydrogenated with bromine and quinoline, 3-chlorocymene is the product (*Jünger*, *Klages*, Ber. **29**, 314). (2) It can be converted into thymol: bromination of menthane in chloroform gives **dibromomenthone** $C_{10}H_{16}Br_2O$, m.p. 80°, which loses 2 HBr to give thymol (*Beckmann*, Ber. **29**, 418). For the conversion of 2,4-dibromomenthone into dihydro-camphorphorone, $C_9H_{16}O$ (p. 56), *semicarbazone*, m.p. 198—199°, see *Wallach*, Ann. **414**, 337.

When reduced with Na + EtOH, *l*-menthone gives *l-menthol and d-neomenthol* (p. 216), and with ammonium formate the formyl compounds of the stereoisomeric menthylamines (p. 227) are formed. Oxidation of menthone with $KMnO_4$ gives β-methyl-adipic acid together with the ketonic acid, β-**methyl-**δ-**isobutyryl-n-valeric acid,** *oxomenthylic acid,*



$$CH_3\cdot CH\!\left<\begin{matrix}CH_2COOH\\ CH_2CH_2CO\cdot CH(CH_3)_2\end{matrix}\right.$$

, (*Manasse*, Ber. **27**, 1820), while Caro's acid gives the ϵ-lactone of **2,6-dimethyl-heptan-3-ol-7-carboxylic acid,**



$$CH_3\cdot CH\!\left<\begin{matrix}CH_2\text{—}CO\text{—}O\\ \qquad\qquad\quad |\\ CH_2\text{—}CH_2\text{—}CH\cdot CH(CH_3)_2\end{matrix}\right.$$

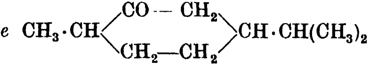
, (*Baeyer*, Ber. **32**, 3621; *Doeuvre*, Bull. **47** (1930), 323). With dilute nitric acid *nitromenthone* is formed, which can be reduced to *aminomenthone* (*Konovalov*, Ber. **31**, 1478). With amyl nitrite and HCl menthone yields *nitroso-menthone* and *menthoximic acid* m.p. 98°; the latter is the oxime of oxomenthylic acid (*Baeyer*, Ber. **29**, 27). When a solution of menthone in aqueous alcohol is exposed to light, the ring opens and *2,6-dimethyl-heptane-7-carboxylic acid* $Me_2CH\cdot(CH_2)_3\cdot CH(Me)\cdot CH_2COOH$ and an *aldehyde* $C_{10}H_{18}O$ are formed; the latter is possibly identical with the menthocitronellal (p. 204) obtained by a rearrangement of menthone oxime (see below) (*Ciamician*, Ber. **40**, 2419). Menthone is oxidised by SeO_2 to buchu-camphor (*Riley*, J. **1932**, 1875).

With sodium and amyl formate menthone yields **hydroxymethylene-menthone** b.p. 121°/12 mm. (*Rupe*, Helv. **9**, 582). **Benzylidene-menthone,** m.p. active 51° and 47°, b.p. 189°/12 mm., can be reduced to *benzyl-menthol* b.p. 180°/9 mm., which can be oxidised to *benzyl-menthone* b.p. 175—178°/10 mm. (*Semmler*, Ber. **37**, 234; *Boedtker*, J. pharm. chim. (8) **6** (1927), 193). When an ethereal solution of menthone is treated with Na + CO_2, a *monocarboxylic* and a *dicarboxylic acid,* m.p. (act.) 144°, are obtained; both of these are probably derivatives of isomenthone (*Gardner*, J. **97**, 1760). **2-Methyl-menthone** (*sym. methyl-menthone*) b.p. 95–97°/12·5 mm., is prepared by hydrogenating hydroxymethylene-menthone; its *tetrahydro-pyrone compound* melts at 99–100°. **4-Methyl-menthone** (*asym. methyl-menthone*) b.p. 100°/17 mm. is obtained from menthone with $NaNH_2$ and MeI; *semicarbazone* m.p. 193–195° (*Cornubert*, Bull. **49** (1931), 1487).

Menthone oxime, m.p. active 61°, *d,l* 82°, b.p. 250°, [α]D–42°, undergoes the Beckmann rearrangement with PCl_5 in chloroform, or with Ac_2O, or conc. H_2SO_4, to give *menthone isoxime* with a rotation of the same sign. This compound is the *ε-lactam* of an *ε-amino-methyl-isopropyl-caproic acid,* m.p. act. 119°, *d,l* 115°, b.p. 295°, [α]D–52·25° (*Read*, J. **127**, 2782). With P_2O_5, both isomers give **menthonenonitrile,** $C_9H_{17}CN$, b.p. 225°, which is hydrolysed to liquid **menthonenic acid,** $C_9H_{17}CO_2H$, a compound with the same constitution as citronellic acid (p. 206), but not identical with it (*Wallach*, Ann. **379**, 227). On reduction, menthonitrile yields *menthonylamine,* and this, with nitrous acid, a *mentho-citronellol* (see above) very similar to citronellol (p. 201) (*Wallach*, Ann. **296**, 120; *v. Braun*, Ber. **62**, 1301). See p. 227 for menthylamine from menthone oxime.

Isomenthone (formula II, p. 230) occurs as the *l*-form in geranium oil from Réunion (*Zeitschel*, J. pr. **133**, 365). It is obtained from menthone by the rearrangement mentioned above, and, together with menthone, from menthenone-3 by catalytic hydrogenation; it can be prepared absolutely pure from isomenthol by careful oxidation with CrO_3. B.p. 212°, d^{15}_{20} 0·902; $[\alpha]^{15}_{D}+91·7°$, n^{20}_{D} 1·45302 (*Zeitschel*, Ber. **59**, 2298; *Read*, J. **1927**, 1276); *semicarbazone* m.p. active 164°, *d,l* (α) 225°, *d,l* (*β*) 178° (*Read*, J. **127**, 2782); *oxime* act. liquid, *d,l* m.p. 99–100°; *oxime hydrochloride* m.p. active 132°, *d,l* 128°. *d*-Isomenthone-oxime hydrochloride is obtained by rearrangement of *l*-menthone-oxime hydrochloride in ether saturated with HCl (*Hiraidzumi*, C. 1931 I 1277). *d,l-Isomenthone isoxime,* m.p. 94–95°. *Benzylidene-(d,l)-isomenthone* b.p. 193–195°/15 mm. (*Read*, J. **125**, 129). Reduction of active isomenthone with Al-isopropoxide gives active *neoisomenthol* m.p. —6° (cf. p. 217); *hydrogen phthalate* m.p. 85–86° (*Schmidt* and *Schulz*, Schimmel Report **1934**, 94; *Read*, J. **1934**, 313).

Tetrahydrocarvone, *carvomenthone*

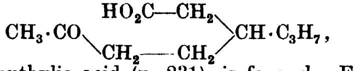


$$CH_3\cdot CH\left\langle\begin{matrix}CO-CH_2\\ CH_2-CH_2\end{matrix}\right\rangle CH\cdot CH(CH_3)_2,$$

b.p. 223°, d^{20} 0·904, n_D 1·45539, occurs as the *l*-form in the essential oil of *Blumea Malcolmii* (*Simonsen*, J. **121**, 876) and has been prepared from tetrahydrocarveol by oxidation (p. 218; *Wallach*, Ann. **414**, 203), from carvone by catalytic reduction (*Armstrong*, Proc. Roy. Soc. **108**, 121, **1925**; *Rupe*, Ann. **459**, 195), and by reduction with sodium in moist ether (p. 237). It can also be obtained from carvacrol (*Grignard*, C. r. **185**, 1522; Belg. **37**, 41); and, together with carvacrol, from carveol and dihydrocarveol (*Treibs*, Ber. **60**, 2335). *Ruzicka* (Helv. **3**, 762) has synthesized it from α-methyl-*β′*-isopropyl-pimelic acid. Its smell is reminiscent of caraway and peppermint. *Semicarbazone* m.p. active 194–195°, *d,l* 174°.

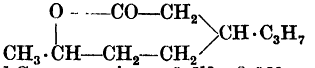
Carvomenthone as ordinarily prepared is a mixture of the two possible geometrical isomers, and either of the two pure compounds gives an equilibrium of the two in presence of NaOEt or H_2SO_4. Pure *l*-carvomenthone, [α]D —7·5°, can be prepared by oxidising *d*-carvomenthol or *l*-neocarvomenthol with CrO_3 (*Read*, J. **1935**, 1138; *W. Huckel*, Ann. **526**, 115) and *l*-isocarvomenthol gives *l*-isocarvomenthone [α]D—56·5°, similarly. The oxime of each of the carvomenthones occurs as two geometrically isomeric oximes, so that there are four *carvomenthone oximes,* two, m.ps. 100–101° and 30–32°, derived from carvomenthone, and two, m.ps. 64–65° and 30–31°, derived from isocarvomenthone (*W. Hückel*, Ann. **526**, 103). The oxime undergoes a Beckmann rearrangement with sulphuric acid, similar to that of menthone oxime, to give an *isoxime,* the *ε-lactam* of *β-isopropyl-ε-aminohexane carboxylic acid* (*Wallach*, Ann. **323**, 323). *Benzylidene compound,* m.p. 175° (*Wallach*, Ann. **305**, 266). Bromination results in

1,3-dibromo-menthanone-2, $C_{10}H_{16}Br_2O$, m.p. active 80–81°, *d,l* 66–67°, which with aqueous potash gives the same products as dibromo-menthone (*Wallach,* Ann. **414**, 355), see also buchu-camphor p. 237. When oxidised with $KMnO_4$ or treated with amyl nitrite and HCl, tetrahydrocarvone breaks down like menthone and *β-isopropyl-δ-acetyl-valeric acid,*



$$\begin{array}{l} \qquad\qquad HO_2C{-}CH_2\diagdown \\ CH_3\cdot CO\diagdown \qquad\qquad\quad CH\cdot C_3H_7, \\ \qquad\qquad CH_2{-}{-}CH_2\diagup \end{array}$$

isomeric with oxomenthylic acid (p. 231), is formed. Energetic oxidation gives isopropyl-succinic acid. With Caro's acid the ε-lactone of *iso-propyl-heptanolic acid*



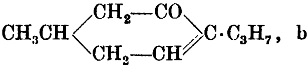
$$\begin{array}{l} \qquad O{-}{-}CO{-}CH_2\diagdown \\ \qquad | \qquad\qquad\qquad CH\cdot C_3H_7 \\ CH_3\cdot CH{-}CH_2{-}CH_2\diagup \end{array}$$

is formed (*Baeyer,* Ber. **29**, 27; **32**, 3629). *l*-Carvomenthone $[\alpha]_D^{17}$—8·02° corresponds sterically to *d*-menthone.

The isomeric *l*-isocarvomenthone, $[\alpha]_D^{20}$—56·5°, n_D^{20} 1·4558, corresponds to isomenthone and can be obtained by oxidation of *l*-isocarvomenthol (*Read,* J. **1935**, 1143). Catalytic reduction of *d*-carvone gives an equilibrium mixture of *l*-carvomenthone and *l*-isocarvomenthone (*Read,* J. **1934**, 227), and the two ketones are interconverted by cold alcoholic NaOEt to an equilibrium mixture which contains 80% carvomenthone.

II. KETOMENTHENES, KETOTETRAHYDRO-p-CYMENES $C_{10}H_{16}O$. —Ketomenthenes contain one double bond; some of them occur in nature and others are obtained by oxidation of the corresponding alcohols.

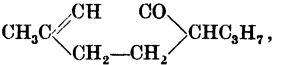
Δ⁴-p-Menthene-3-one



$$CH_3CH\left\langle\begin{array}{l} CH_2{-}CO \\ CH_2{-}CH \end{array}\right\rangle C\cdot C_3H_7,$$

b.p. 213°, d^{20} 0·918, n_D 1·4720; its *oxime, "nitroso-menthene",* is obtained from menthene nitroso-chloride (p. 214) by removal of HCl (*Wallach,* Ann. **305**, 272; **362**, 275).

Piperitone, *Δ¹-p-menthene-3-one,*

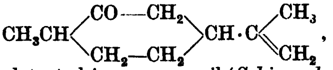


$$CH_3C\left\langle\!\!\begin{array}{l} CH \quad CO \\ CH_2{-}CH_2 \end{array}\!\!\right\rangle CHC_3H_7,$$

b.p. 236°, d_4^{20} 0·9331, n_D^{20} 1·4845. Its *d*-form, $[\alpha]_D^{20}$ + 49·13°, occurs in Japan peppermint oil and in the oil of *Andropogon iwarancusa*; its *l*-form, $[\alpha]_D^{20}$—51·53°, occurs abundantly in the oils of many species belonging to the peppermint group of *Eucalyptus,* from which it can be separated by means of its compound with orthophosphoric acid (Brit. Pat. 410,813; U.S.A. Pat. 1,960,134). Its smell is reminiscent of that of camphor and peppermint. It racemises when heated at ordinary pressure, and still more rapidly when treated with alkali, so that derivatives prepared from it are often found to have lost their activity. The *d,l-semicarbazone* occurs in two forms, m.p. α, 226–227°, β, 174–176°, both of which are decomposed into the same *d,l-Δ¹-menthenone-3* (*Read,* J. **123**, 2267; Chem. & Ind. **42**, 339). *d,l-Oxime* m.p. α, triclinic, 118–119°; β, monoclinic, 88–89°; both yield the *d,l-oxime hydrochloride,* m.p. 157°. With an excess of hydroxylamine in alkaline solution two ***hydroxylamino-oximes*** m.ps. α 176° and β 186° are formed. ***Bisnitroso derivative,*** m.p. 97–98°. Bromo derivatives, ***Wallach,*** Ann. **414**, 287. Photo-polymerisation, *Treibs,* Ber. **63**, 2738; autoxidation id. ib. **66**, 610. It gives addition compounds with sodium sulphite and bisulphite, and also with orthophosphoric acid; these can be used for its separation from mixtures. Its constitution is proved by its close relation to thymol, into which it is converted on boiling with $FeCl_3$, and also by the products of its oxidation, which include α-hydroxy-α-methyl-α′-isopropyl-adipic acid, α-isopropyl-γ-acetyl-butyric acid and α-isopropyl-glutaric acid, and finally by its formation from 1,3,4-p-menthanetriol (p. 222) by heating with HCl (*Wallach,* Ann. **362**, 271); p-cymene is a by-product of the latter reaction. The first total synthesis has been carried out recently (***Walker,*** J. **1935**, 1585) from Na-isopropyl-acetoacetic ester and β-chlorethylmethyl-ketone by ring closure and hydrolysis. $KMnO_4$ in neutral solution oxidises piperitone to diosphenol (buchu-camphor) (*Stephan*, J. pr. **129**, 145), and O_2 in alcoholic alkaline solution first to piperitone oxide, and then to a hydroxy-cyclopentane-carboxylic acid, which loses water and gives *piperitolenic acid* (p. 68).

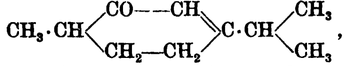
The reduction of Δ^1-menthenone-3 with Na and EtOH does not give the corresponding alcohol (cf. *Kimura*, J. chem. Soc. Japan **33** [1930], 301 B), but a mixture of menthol and isomenthol (*Read*, J. **1927**, 1276), while in catalytic reduction isomenthone is the chief product, together with some thymol; the former can be converted into menthone by the action of alcoholic potash (p. 230) (*Read* et al., J. **123**, 2916). Δ^1-Menthenone-3 is therefore industrially important as a starting material for the manufacture of "synthetic" menthol, and also of "synthetic" thymol. For its reactions with aldehydes see *Earl*, J. **1926**, 2072; with Grignard reagents, *Read*, J. **1929**, 2165; pyrolysis, *Treibs*, Ber. **61**, 683.

Dihydrocarvone, $\Delta^{8(9)}$-*menthene-2-one*



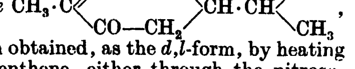
b.p. 221°, d_{19} 0·928, n_D^{15} 1·4723, has been detected in caraway oil (*Schimmel*, Report April **1905**, 20). The *d*- and *l*-forms can be obtained from the corresponding dihydrocarveols by oxidation or from the carvone of the opposite sign of rotation by reduction with zinc dust and alcoholic potash (*Wallach*, Ann. **279**, 377); also by electrolytic reduction of carvoxime (*Rupe*, Ber. **47**, 2150). *Semicarbazone*, m.p. act. 189–191°, *d,l*, 188°; *oxime* m.p. act. 88°, *d,l* 115°. *Benzylidene compound* b.p. 187–190°/10 mm. (*Wallach*, Ann, **305**, 268). When dihydrocarvone is boiled with $FeCl_3$, carvacrol is produced, cf. carvenone and carone. By successive oxidation with potassium permanganate and chromic acid dihydrocarvone is converted into *2,5-methyl-acetyl-cyclohexanone* (p. 222; *Tiemann*, Ber. **28**, 2147; *Wallach*, ib. 2704). Photolysis, see *Ciamician*, Ber. **41**, 1928.

Carvenone ("carveol"), Δ^3-p-*menthene-2-one*



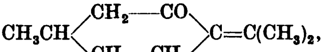
b.p. 232°, d 0·927, n_D 1·4822, has been obtained by heating 1,2,8- or 1,2,4-p-menthane-triol (p. 222) with dilute sulphuric acid, together with cymene, by the isomeric change of dihydrocarvone or carone (p. 248) in presence of mineral acids or formic acid, by treating camphor or, better, dichloro-camphane (p. 274) with sulphuric acid, and also by reducing α-terpinene nitrosite (p. 211) with zinc and glacial acetic acid (*Stephan*, J. pr. **60**, 261; *Bredt*, Ann. **314**, 369). It racemises very easily and only the *d,l*-form has been obtained. *Oxime*, m.p. 91°. *Hydroxylamino-oxime*, m.p. 163°. *Semicarbazone*, m.ps. 202° and 154°. It is closely related to carvotanacetone (see below). Boiling ferric chloride oxidises carvenone to carvacrol (vol. III), while heating with P_2O_5 gives cymene. It is oxidised by permanganate to α-hydroxy-α-isopropyl-α′-methyl-adipic acid, m.p. 136—137°, γ-isobutyryl-α-methyl-butyric acid and α-methyl-glutaric acid (*Bredt*, Ann. **314**, 380). With PCl_5 it gives *monochloro-carvenene* $C_{10}H_{15}Cl$, b.p. 95–98°/10 mm., which on reduction with Na and EtOH yields α-terpinene (p. 210; *Semmler*, Ber. **41**, 4477). Autoxidation, *Treibs*, Ber. **65**, 163; it behaves towards H_2O_2 like piperitone (id. **66**, 1485).

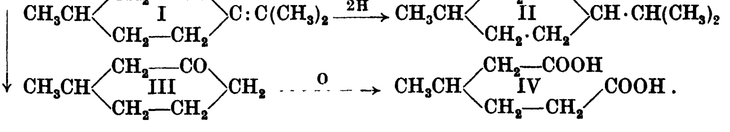
Carvotanacetone, Δ^1-p-*menthene-6-one*



b.p. 228°, d^{21} 0·938, n_D 1·47926, has been obtained, as the *d,l*-form, by heating thujone (p. 242) to 280°, from carvomenthene, either through the nitrosochloride and carvotanacetone *oxime*, m.p. *d,l* 93–94° (*Wallach*, Ann. **381**, 51), or more conveniently by oxidising carvomenthene with SeO_2 (*Borgwardt*, Am. **56**, 1185; *Tabuteau*, C. r. **200**, 244), and, finally, from carvone by reduction with H_2 and PtO_2 (*Dulou*, Bull. Pin **1934**, 49). *Semicarbazone*, m.p. 177°

(*Wallach*, Ber. **28**, 1959). *d*-Carvotanacetone $[\alpha]_D^{20}$ + 59·55° is the chief constituent of the essential oil of *Blumea Malcolmii*. *Oxime* m.p. 77°; *semicarbazone*, m.p. 173°; *hydroxylamino-oxime*, m.p. 96°; *phenylhydrazone* m.p. 92° (*Simonsen*, J. **127**, 876). Preparations of smaller rotatory power have been obtained by the careful reduction of α-phellandrene nitrite (*Wallach*, Ann. **336**, 36). A dextrorotatory carvotanacetone has also been obtained by reducing carvone hydrobromide with zinc dust and MeOH (*Harries*, Ber. **34**, 1924). A very simple method of preparing both active and *d,l*-carvotanacetone is from tetrahydrocarvone which is first converted into its 1-monobromide (*Wallach*. Ann. **414**, 353); or carvomenthene is oxidised with SeO_2 (p. 214), in which reaction *carvotanacetol*, b.p. 86°/3 mm, is a by-product (*Borgwardt*, l.c.). Carvotanacetone forms a compound with sodium sulphite. Like carvone (p. 237), it unites with H_2S to form the compound $(C_{10}H_{16}O)_2H_2S$, m.p. act. 225° and *d,l* 205°. $KMnO_4$ oxidises it to β-isopropylglutaric acid m.p. 103–104° (*Simonsen*, J. **121**, 876), and to pyruvic and isopropyl-succinic acids (*Semmler*, Ber. **33**, 2457). With PCl_5 it gives *monochloro-phellandrene* $C_{10}H_{15}Cl$, b.p. 108°/15 mm., which is reduced to α-phellandrene by zinc dust in MeOH (*Harries*, Ber. **38**, 1832). Autoxidation of carvotanacetone yields the oxide, which rearranges to the unstable *2-hydroxy-carvotanacetone*, m.p. 181° (*Treibs*, Ber. **66**, 1484).

Pulegone, *$\Delta^{4(8)}$-p-menthene-3-one*, , b.p. 221° and b.p. 103°/17 mm., d_4^{17} 0·939 (*Doeuvre*, Bull. 2 [1935], 298), is contained in the essential oils from *Mentha pulegium* and *Hedeoma pulegioides*, which are sold under the name of pennyroyal oil, and is the chief constituent of the essential oil of *Mentha canadensis* L. (*Braun*, J. Am. Pharm. Ass. **15**, 337). Pulegone forms an addition compound with sodium bisulphite (*Tiemann*, Ber. **30**, 25) and combines with sulphur dioxide to *pulegone-sulphonic acid* (*Wallach*, C. 1920 I 671), an acid forming very stable salts. With conc. H_2SO_4 and Ac_2O *cyclopulegenol sulphonate*, $C_{10}H_{14}O_3S$, m.p. 35°, is formed, which on heating dissociates to menthofuran (p. 226) (*Treibs*, Ber. **70**, 85). Like other α, β-unsaturated ketones, pulegone combines with sodio-malonic ester (*Vorlander*, Ann. **345**, 158; *May*, ib. 188), with KCN (*Clarke*, J. **89**, 1869) and with sodio-cyanacetic ester (*Kon*, J. **1926**, 3101). *Semicarbazone*, m.p. act. 172–173°; for an isomeric pyrazoline derivative see *Busse*, Ber. **63**, 2209. *Bis-nitroso derivative*, m.p. active 85° (*Gordon*, Am. Pharm. **99**, 524). *Hydrobromide*, m.p. 140–141°. *Dinitro-phenylhydrazone* m.p. 142°. Pulegone (I) is converted by the addition of hydrogen into a mixture of menthone and isomenthone (II) (p. 230); passing the vapour over Cu or Ni at 280° gives the same mixture, together with thymol (*Treibs*, Ber. **60**, 2338). Reduction to *pulegol* p. 225. On oxidation pulegone breaks down into β-methyladipic acid (IV) and acetone; for the action of benzoyl peroxide see *Prileshajev*, Bull. **41** (1927), 687. When heated with formic acid or with water under pressure, it is decomposed into acetone and 3-methyl-cyclohexanone (III) (p. 110); the latter also gives β-methyladipic acid on oxidation (*Wallach*, Ann. **289**, 337; Ber. **32**, 3338):

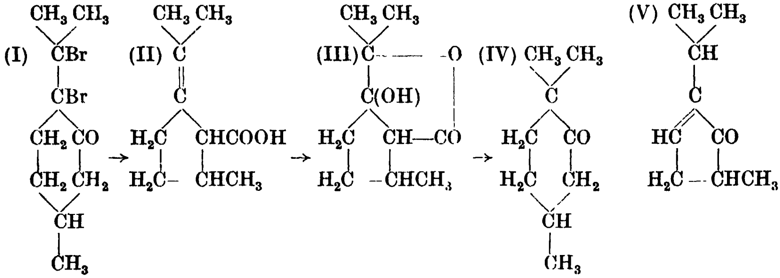


If, on the other hand, methyl-cyclohexanone and acetone are condensed by means of alkalies, a position-isomer of pulegone, b.p. 215°, is formed (*Wallach*, Ann. **394**, 380). Like menthone, pulegone is converted into its enol form (*benzoate*, m.p. 230°) by the action of Grignard reagents, and this reverts extraordinarily easily into the keto form (*Grignard*, Bull. Belg.

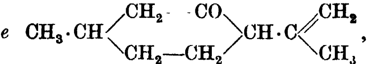
36, 97; *Blanchon*, C. 1930 I 1117). *Pulegone oxide* m.p. 40° is formed by the action of H_2O_2 and potash on pulegone in MeOH (*Treibs*, Ber. **66**, 1492).

If pulegone dibromide (I) is heated with a solution of NaOMe, *pulegenic acid* (II), $C_{10}H_{16}O_2$, is formed, the six-membered ring being converted into a five-membered ring (*Wallach*, Ann. **414**, 233; *Rupe*, Helv. **11**, 463). This acid is oxidised by $KMnO_4$ to a hydroxy-lactone (III), which, when heated with sulphuric acid (2 : 1), loses CO_2 and undergoes a rearrangement to give 3,6,6-*trimethyl-cyclohexanone*, *pulenone* (IV), the ring being enlarged to a six-membered ring (*Wallach*, Ann. **329**, 82; *Meerwein*, Ann. **376**, 154). For the synthesis see *Cornubert*, Bull. **49** (1931), 1238.

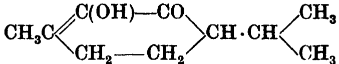
From pulegenic acid the hydrocarbon *pulegene* C_9H_{16}, b.p. 139°, d 0·791, can be obtained by elimination of CO_2. Its nitrosochloride can be converted into *pulegenone*, $C_9H_{14}O$ (V), b.p. 190°, a ketone closely related to camphorphorone (p. 305) (*Wallach*, Ann. **327**, 115; **418**, 46, 49).



Benzylidene-pulegone, b.p. 203°/13 mm. (*Wallach*, Ann. **305**, 267; *Rupe*, Helv. **11**, 463). When pulegone is treated with hydroxylamine in presence of alkalies, the double bond migrates and isopulegone oxime (see below) is formed. Under other conditions hydroxylamine addition products are formed: *pulegone-hydroxylamine*, $C_{10}H_{17}O(NHOH)$, m.p. 157°, which can be oxidised to *nitrosomenthone*, m.p. 35°, and reduced to *aminomenthone* (*Harries*, Ber. **31**, 1809; **32**, 3365), and also *pulegone-hydroxylamine-oxime*, $C_{10}H_{17}(NHOH):(NOH)$, m.p. 118°, which is reduced by Na and alcohol to *3,3-diamino-menthane* (*Semmler*, Ber. **38**, 146).

Isopulegone, $\Delta^{8(9)}$-p-*menthene-3-one*  $CH_3\cdot CH\begin{matrix}CH_2-CO\\ CH_2-CH_2\end{matrix}CH\cdot C\begin{matrix}CH_2\\ CH_3\end{matrix}$, b.p. 101–102°/17 mm., d_4^{20} 0·92086, n_D^{20} 1·46669, may be obtained from its *oxime* m.p. act. 121°, *d,l* 140°, by heating with oxalic acid (*Wallach*, Ann. **365**, 247), or from pulegone hydrobromide with basic lead nitrate, or best by oxidising the corresponding alcohol *isopulegol*, the isomerisation product of citronellal (p. 203). It contains two asymmetric C-atoms, and thus should exist in the same number of isomeric forms as menthanone-3 (p. 230). The substance obtained from isopulegol seems to correspond sterically to menthone (*Pickard*, J. **117**, 1248). From the nature of the ozonisation products and from absorption measurements isopulegone is assumed to be present in natural pulegone (*Savard*, C. r. **186**, 1436, 1738; *Rupe*, Ann. **459**, 192; but see *Hugh, Kon, Linstead*, J. **1927**, 2585). Unlike pulegone, it is not attacked by Al amalgam. The *enolic form* is very unstable and is obtained by treatment with Grignard reagents, as in the case of menthone and pulegone; b.p. 80–81°/6 mm., d_4^{14} 0·8965, n_D^{14} 1·46732 (*Grignard*, C. r. **182**, 422). Isopulegone is converted into pulegone by baryta water and still more rapidly by NaOEt (*Harries*, Ber. **32**, 3357; *Hugh*, l.c.); for its conversion into menthofuran, with cyclopulegenol-sulphonic ester as an intermediate, see *Treibs*, Ber. **70**, 87. *Semicarbazone*, m.ps. act. 173° and 156° (*Doeuvre*, Bull. **53** (1933), 589), *d,l* 183°.

α-Santolinonene is formulated as a *$\Delta^{1(7)}$-p-menthene-2-one.* It occurs in the oil of *Santolina chamaecyparissus* and is only known in the form of its *hydroxylamino-oxime*, m.p. *d,l* 190°, act. 171° (*Francesconi*, Gazz. **45** I 35, 167).

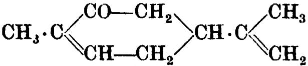
2,3-Diketomenthane is extremely unstable; like other cyclic o-diketones (cf. e.g. "isocamphor-quinone") it passes at once into a stable mono-enol form, **2-hydroxy-Δ^1-p-menthene-3-one** 

$$CH_3C\left\langle\begin{matrix}C(OH)-CO\\CH_2-CH_2\end{matrix}\right\rangle CH\cdot CH\left\langle\begin{matrix}CH_3\\CH_3\end{matrix}\right.,$$

m.p. 84°, b.p. 110°/10 mm. (*Auwers*, Ber. **57**, 1106). This compound has been separated from buchu leaves (*Barosma betulina* etc.) and has therefore been called **buchu-camphor**; it is also known as **diosphenol**. In its behaviour it shows both ketonic and phenolic character. It gives a green colour with ferric chloride and forms an acetate, a benzoate, a *phenylurethane*, m.p. 113–114°, and a *monoxime*, m.p. 125°. A *dioxime*, m.p. 197°, can be obtained under special conditions (*Wallach*, Ann. **437**, 170). Diosphenol forms thymol and a little carvacrol when heated with conc. HCl. The enolisation of 2,3-diketomenthane might give rise, not only to diosphenol, but also to *3-hydroxy-Δ^3-menthene-2-one*, and certain reactions can be regarded as giving evidence for the transitory existence of this compound, for example, the formation of carvacrol, and the formation of hydroxy-tetrahydro-carvone in the catalytic reduction (*Cusmano*, Lincei (5) **30** II 224). It is, however, extremely unstable, since 3,4-dihydroxy-menthanone-2, obtained from carvenone, and 1,2-dihydroxy-menthanone-3, obtained from Δ^1-menthenone-3, both yield buchu-camphor by elimination of water (*Wallach*, Ann. **437**, 148). Ozonisation gives α-isopropyl-γ-acetyl-butyric acid m.p. 41°, and reduction with Na and EtOH 2,3-p-menthane-diol; the latter is oxidised by $KMnO_4$ to α-methyl-α′-isopropyl-adipic acid (*Auwers*, Ber. **57**, 1106). Dehydrogenation in the presence of Na gives 2,3-dihydroxy-p-cymene, together with other aromatic compounds and tetrahydrocarvone (*Cusmano*, Gazz. **60**, 105), while catalytic hydrogenation can give either 2-hydroxymenthone-3 or 2,3-menthane-diol, depending on the conditions (*Walker*, J. **1934**, 238). *Monobromo-buchu-camphor*, m.p. 77°, has been converted into methyl-isopropyl-pyrocatechol (*Paolino*, Lincei (5) **28** II 82). *Dibromo-buchu-camphor*, m.p. 44–45°. Buchu-camphor undergoes the benzilic acid rearrangement when heated with potash under pressure, the ring contracting to form 1-methyl-3-isopropyl-cyclopentan-2-ol-2-carboxylic acid, which can be oxidised to dihydrocamphor-phorone (*Wallach*, Ann. **414**, 346).

Buchu-camphor has been synthesised: from hydroxymethylene-menthone (p. 231) by ozonisation (*Semmler*, Ber. **39**, 1158); from menthone with $FeCl_3$ (*Asahina*, J. Pharm. Japan **1922**, No. 482) or with SeO_2 (*Riley*, J. **1932**, 1875); from dibromo-tetrahydrocarvone, or dibromo-menthone, with potash (*Wallach*, Ann. **437**, 148); and from piperitone oxide with H_2SO_4 (*Treibs*, Ber. **66**, 619).

III. KETOMENTHADIENES, KETODIHYDRO-p-CYMENES $C_{10}H_{14}O$. —The most important member of this group is the ketone *carvone*, which was formerly called *carvol*, because of its close relationship to carvacrol, with which it is isomeric, and to limonene. As with these compounds, carvone is known in the three forms, *d*-, *l*- and *d,l*.

Carvone, $\Delta^{6,8(9)}$-p-*menthadiene-2-one* 

$$CH_3\cdot C\left\langle\begin{matrix}CO-CH_2\\CH-CH_2\end{matrix}\right\rangle CH\cdot C\left\langle\begin{matrix}CH_3\\CH_2\end{matrix}\right.,$$

b.p. 230°, $[\alpha]_D \pm 62{\cdot}3°$, d^{15}_{15} 0·9652, occurs as the *d*-form in caraway oil, dill oil and other oils. The *l*-form is a constituent of the oils of spearmint and *kuromoji*. It is obtained in a pure state by distilling its H_2S-compound (see below) with aqueous potash (*Wallach*, Ann. **305**, 224). *Semicarbazone*, m.p. active, 163° and 142° (*Rupe*, Ber. **39**, 2372). When heated with potash, phosphoric acid or formic acid (*Klages*, Ber. **32**, 1517) it is converted into the isomeric carvacrol (vol. III); hence it has been deduced that the CO-group in carvone, like the OH-group in carvacrol, occupies the ortho position relative to the methyl group. With PCl_5 carvone yields a dichloride $C_{10}H_{14}Cl_2$, from which 2-chloro-cymene is obtained by distillation with quinoline (*Baeyer*, Ber. **32**, 2555). The products obtained on reduction depend on the conditions; the corresponding alcohols (see below), dihydrocarveol (p. 225), dihydrocarvone (p. 234), and bimolecular *α-dicarvelone* $(C_{10}H_{15}O)_2$, m.p. act. 148—149°, *d,l* 121°, can be formed (*Wallach*, Ann. **403**, 96). Catalytic hydrogenation with H_2 and Ni or Pd leads primarily to carvotanacetone, then to tetrahydrocarvone (cf. inter al. *Armstrong*, Proc. Roy. Soc. **108**, 121) and can be carried still further to give carvomenthol (*Vavon*, C. r. **158**, 409; *Paolino*, Lincei (5) **30** II 371; C. 1935 II 3516). Carvone reacts with ammonium formate to give dihydrocarvylamine (p. 228). $KMnO_4$ oxidises carvone to *hydroxy-terpenylic acid* $C_8H_{12}O_5$ which easily passes into a *dilactone* $C_8H_{10}O_4$ m.p. 129° (*Best*, Ber. **27**, 3333; *Tiemann*, ib. **28**, 2148). In sunlight carvone undergoes a curious isomeric change into a substance called "*carvone-camphor*", a ketone $C_{10}H_{14}O$, m.p. 100° (*Sernagiotto*, Gazz. **48** I 52; *Treibs*, Ber. **63**, 2738; id. J. pr. **138**, 299). Ozonisation, see *Harries*, C. 1916 II 993; autoxidation produces *carvone oxide* $C_{10}H_{14}O_2$, b.p. 120—122°/15 mm., which changes easily into hydroxy-carvone (see below) and further into cymorcinol, a derivative of cymene (*Treibs*, J. pr. **138**, 284; Ber. **65**, 1314). Carvone combines with H_2S; the compound m.p. act. 211°, *d,l* 189-190° consists of 2 mols of carvone to one of H_2S and contains the keto group intact (*Macbeth*, J. **1934**, 1147; see, however, *Dulou*, Bull. Pin **1934**, 205). Carvone also combines with HCl, HBr, HCN and Br_2 (*Wallach*, Ann. **286**, 119; **305**, 235; *Lapworth*, J. **89**, 1819); for the formation of *carvenolide*, $C_{10}H_{14}O_2$, from *carvone tribromide*, m.p. (*d,l*) 76°, see *Wallach*, Ann. **305**, 245; **414**, 240. With $NaHSO_3$, the sodium salt of *carvone-dihydro-disulphonic acid* is obtained (*Labbé*, Bull. **23** [1900], 280). On shaking with dilute H_2SO_4 carvone takes up one mol. H_2O to form *hydroxy-dihydrocarvone* or *carvone hydrate*, m.p. 41—42° (*Rupe*, Ber. **38**, 1719; *Knoevenagel*, ib. **39**, 677).

With aceto-acetic ester in the presence of NaOEt it forms a bicyclic condensation product (*Rabe*, Ber. **36**, 225). For its reactions with Grignard compounds, see *Rupe*, Ber. **47**, 3064; *Semmler*, Ber. **50**, 1833; *carvone-enol*: *Grignard*, C. 1930 I 1116.

d,l-Carvone, b.p. 230°, d_{15}^{15} 0·9645, *semicarbazone*, m.p. 155°, occurs in gingergrass oil and is obtained by mixing *d*- and *l*-carvone, by oxidising carveol methyl ether (p. 227), by the autoxidation of limonene (*Blumann*, Ber. **47**, 2623) and by oxidising dipentene with CrO_3 and acetic anhydride in chloroform (*Treibs*, Ber. **61**, 459). In the two last reactions *d,l*-carveol is formed at the same time, cf. the autoxidation of pinene to verbenol and verbenone. For the formation of carvone from α-terpineol, see *Wallach*, Ann. **291**, 342.

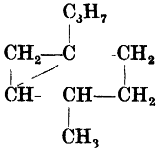
The connecting links between the three forms of carvone and those of limonene are the three *carvoximes*, obtained from the carvones with hydroxylamine and from the limonene nitrosochlorides with alcoholic potash. *d*-Carvone is related to *l*-limonene, and *l*-carvone is related to *d*-limonene, since *l*-limonene nitrosochloride gives *d*-carvoxime, and *d*-limonene nitrosochloride gives *l*-carvoxime (p. 208).

d-Carvoxime, $[\alpha]_D + 39{\cdot}71°$, and **l-carvoxime,** $[\alpha]_D - 39{\cdot}34°$, are each known in two forms, m.ps. (α) 72° and (β) 58°. *d,l-Carvoxime*, m.p. 93°, is obtained from dipentene nitrosochloride (p. 209). Carvoxime undergoes rearrangement in presence of conc. sulphuric acid to p-aminothymol (cf. the rearrangement of N-phenylhydroxylamine to p-aminophenol) (*Wallach*, Ann. **279**, 356). **Hydroxylamino-carvoxime,** $C_{10}H_{15}(NOH)NHOH$, a syrup, can be oxidised to the dioxime of *$\Delta^{8(9)}$-p-menthene-dione-2,6*, $C_{10}H_{14}O_2$, m.p. 185–187°; this diketone is formed directly from carvone by atmospheric oxidation in the presence of baryta, and is called **hydroxy-carvone,** since its reactions are those of a mono-enol (*Harries*, Ber. **34**, 2105; *Treibs*, Ber. **65**, 1314).

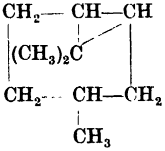
C. BICYCLIC TERPENES

The terpenes of this group are distinguished from the monocyclic terpenes in that they are capable of adding on only two univalent atoms or groups of atoms. They thus contain two carbon rings. These bicyclic terpenes can be converted into monocyclic terpenes in several ways, like the latter, they are closely related to p-cymene and can usually be converted into it with ease.

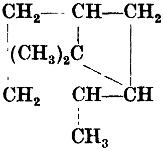
Their dihydro-derivatives are related to hexahydrocymene, in that either the cyclohexane carbon atom carrying the isopropyl group is linked to the 3-carbon atom by a diagonal bond, whereby a ring-system composed of a three-ring and a five-ring is formed as in the **sabinane** or **tanacetane** group, or the central carbon atom of the isopropyl group is joined to a second cyclohexane carbon atom. According to whether this linking takes place in the 1,2, 1,3-, or 1,4-position the parent hydrocarbon of the **carane, pinane,** or **camphane** group is formed:



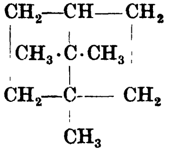
Sabinane



Carane



Pinane



Camphane

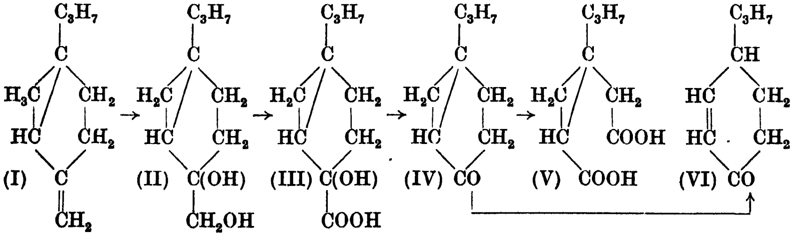
On the basis of their carbon-skeletons the sabinane and carane derivatives belong respectively to the 0:1:3-bicyclohexane and 0:1:4-bicycloheptane groups of condensed ring systems. Pinane and camphane derivatives, on the other hand, contain bridged rings (p. 179), formed from a six-ring with a single-membered carbon-bridge in the 1,3- or 1,4-position; they are derivatives of 1:1:3-bicycloheptane and of 1:2:2-bicycloheptane, respectively (p. 185). While these ring-systems are stable to the ordinary additive reagents and are thus readily distinguished from rings containing double bonds, yet at high temperatures and especially by the action of hydrating agents they are often converted with surprising ease into derivatives of the monocyclic terpenes.

I. SABINANE OR TANACETANE GROUP

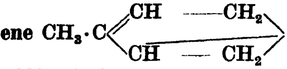
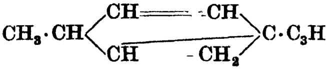
The compounds of this group, of which thujone or tanacetone is the most important member, contain as their carbon skeleton a condensed ring system, a five-ring carrying a three-ring in the 1:2-position. They may be degraded by oxidation to cyclopropane carboxylic acids.

1. Hydrocarbons.—The parent hydrocarbon, 0:1:3-bicyclohexane, *norsabinane*, b.p. 78·5—79·5°/740 mm., d_4^{18} 0·8199, n_D^{18} 1·4326, has been obtained synthetically (p. 53; *Konovalov*, C. r. **183**, 40). Other hydrocarbons of the series are sabinene and the two thujenes; all three contain the same carbon skeleton and differ only in the position of the double bond, since cautious reduction gives the same bicyclic hydrocarbon, $C_{10}H_{18}$, sabinane or thujane.

Sabinene (I) $C_{10}H_{16}$, b.p. 163–165°, d^{20} 0·842, n_D 1·4678 (*Padmanabhan* and *Jatkar*, Am. **57**, 334), (synthetic: b.p. 163°, d^{18} 0·8455, n_D 1·4668) is present as its *d*-form in savin oil, Ceylon cardamom oil, marjoram oil (*Wallach*, Ann. **357**, 77), pilea oil (*Semmler*, Ber. **40**, 2963), Indian juniper oil and the oil of the Himalayan cypress (*Simonsen*, J. Abs. 1923 I 1106); the *l*-form occurs in savin oil and the oils of *Xanthoxylum budrunga* and *rhetsa*, and the *d,l*-form in the oil of *Murraya Koenigii*. It is detected by degradation to the oxidation products, sabinenic acid and sabina ketone, which are described below. It has been synthesised by treatment of sabina ketone with magnesium methyl iodide, followed by dehydration of the methylsabinaketol so formed (*Drotschmann*, Sch. & Co., Report **1925**, 174). With dry hydrogen chloride in CS_2 sabinene yields terpinene monohydrochloride, and with hydrogen halides in glacial acetic acid the corresponding terpinene dihydrohalides (p. 211). With dilute sulphuric acid in the cold it yields optically active terpinen-4-ol and 1:4-terpin and when heated, α-terpinene. On oxidation with $KMnO_4$, sabinene behaves like the majority of other terpenes containing a semicyclic methylene group (cf. β-pinene and camphene). *Sabinene glycol* (II), m.p. (active) 54°, is first formed, and then an α-hydroxy-acid, *sabinenic acid* (III), m.p. 57° (*d,l*-, m.p. 85°), distinguished by its sparingly soluble sodium salt; finally, a ketone with one carbon atom less, *sabina ketone* (IV), m.p. 17°, b.p. 218–219°, d_{19} 0·956, n_D^{19} 1·4704, is formed. Decomposition of sabina ketone *semicarbazone*, m.p. 141–142°, with oxalic acid yields sabina ketone, but, if dilute sulphuric acid is used, the 3-ring opens and the product is the isomeric Δ^3-4-isopropylcyclohexenone; when this compound is heated, it rearranges to Δ^2-isopropylcyclohexenone (VI) (p. 116). This ketone is also formed from sabina ketone by heating with aqueous or alcoholic sulphuric acid. Further degradation of sabina ketone affords *α-tanacetonedicarboxylic acid* (V) (p. 32) (*Wallach*, Ann. **359**, 266; *Semmler*, Ber. **35**, 2045):

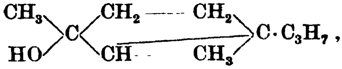


For the application of sabina ketone to the synthesis of β-terpinene see p. 211. With CrO_2Cl_2 sabinene gives an addition compound, $C_{10}H_{16}\cdot 2CrO_2Cl_2$, which is decomposed by water to *sabinenilanaldehyde*, a viscous liquid of characteristic odour, b.p. 215–217°; *semicarbazone*, m.p. (active) 145–146°. Oxidation, in the air or with dilute nitric acid, yields *sabinenilanic acid*, m.p. 175–176°. In the reaction with the chromyl chloride a ketone isomeric with sabina ketone, isopropylidene-cyclohexanone (p. 111) is formed, as well as the addition product (*Henderson*, *Robertson* and *Brown*, J. **121**, 2717).

α-Thujene  $CH_3\cdot C\left\langle\begin{array}{c}CH\text{---}CH_2\\ \hline CH\text{---}CH_2\end{array}\right\rangle C\cdot C_3H_7$, b.p. 152°, d_{30}^{30} 0·8314, n_D^{20} 1·4502, $[\alpha]_D$ + 37·69° (*Padmanabhan* and *Jatkar*, Am. **57**, 334), which forms the principal constituent of the terpene fraction of the gum of *Boswellia serrata*, is obtained ($[\alpha]_D$ — 37·20°) by decomposition of the xanthogenate of d-thujyl alcohol (see below) (*Tchugaev* and *Fomin*, Ber. **45**, 1297). If thujyl alcohol from the reduction of α-thujone or dihydrosabinol (p. 242) (*Henderson* and *Robertson*, J. **123**, 1713) is used in this reaction, a mixture of α-thujene and **β-thujene,**  $CH_3\cdot CH\left\langle\begin{array}{c}CH=\!=CH\\ \hline CH\text{---}CH_2\end{array}\right\rangle C\cdot C_3H_7$ (?), b.p. 147°, d_{20} 0·8202, n_D^{20} 1·44708, $[\alpha]_D$ + 110·78°, is obtained (*Tchugaev* and *Fomin*, Ber. **45**, 1297). The same mixture is obtained by exhaustive methylation of thujylamine, followed by heating the resulting quaternary ammonium base (*Tchugaev*, Ber. **34**, 2276; **37**, 1481). α-Thujene gives α-thujaketonic acid (p. 243) on oxidation with $KMnO_4$ and combines with 2 mols. of hydrogen halide to the corresponding terpinene dihydrohalide. On shaking with dilute sulphuric acid it behaves like sabinene and gives active terpinen-4-ol and 1:4-terpin (*Wallach*, Ann. **350**, 166; **356**, 201). **Isothujene,** b.p. 172–175°, d_{20} 0·840, n_D 1·4761, is isomeric with both these hydrocarbons, and is obtained by dry distillation of α-thujylamine hydrochloride (*Wallach*, Ann. **286**, 99); it is probably 1:2-dimethyl-3-isopropyl-cyclopentadiene.

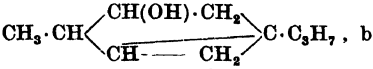
Sabinane, *thujane*, *tanacetane*, $C_{10}H_{18}$, b.p. 157°, d_4^{15} 0·820, n_D^{15} 1·442, is obtained by hydrogenation of sabinene and α- and β-thujene in the presence of Pt-black (*Tchugaev* and *Fomin*, C. r. **151**, 1058; *Zelinsky* and *Levina*, Ann. **476**, 60), and from thujone hydrazone by heating with sodium methoxide under pressure (*Semmler* and *Feldstein*, Ber. **47**, 388). Hydrogenation of sabinene with Pd-black causes fission of the 3-ring, yielding *1:2-dimethyl-3-isopropylcyclopentene*, b.p. 156–156·6°/757·5 mm., d_4^{15} 0·811, and *1:2-dimethyl-3-isopropylcyclopentane*, b.p. 161·4–161·9°/758 mm., d_4^{15} 0·7929 (*Richter*, *Wolff* and *Presting*, Ber. **64**, 871).

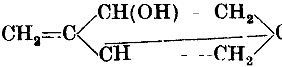
2. Alcohols. — Sabinene hydrate, *methylsabinaketol*, $C_{10}H_{18}O$



$$\begin{matrix}CH_3\\HO\end{matrix}\!>\!C\left\langle\begin{array}{c}CH_2\text{---}CH_2\\ \hline CH\text{---}CH_3\end{array}\right\rangle C\cdot C_3H_7,$$

m.p. 39°, b.p. 195–201°, is formed, together with α-terpinene, by the action of magnesium methyl iodide on sabina ketone (p. 240). Cautious dehydration yields sabinene (p. 240), but more energetic dehydration leads to terpinene. With hydrogen bromide in glacial acetic acid terpinene dihydrobromide is formed; shaking with dilute sulphuric acid yields optically active terpinen-4-ol and 1:4-terpin (*Wallach*, Ann. **357**, 64).

Thujyl alcohol, *tanacetyl alcohol*,  $CH_3\cdot CH\left\langle\begin{array}{c}CH(OH)\cdot CH_2\\ \hline CH\text{---}CH_2\end{array}\right\rangle C\cdot C_3H_7$, b.p. 206–210°, occurs, partly in the free state and partly as the esters of acetic, isovaleric and palmitic acids, in oil of wormwood (*Wallach*, Ann. **272**, 109) and in the oil of some species of *Artemisia* (*Assenzio italiano*; *Paolini* and *Lomonaco*, Lincei (5) **23**, II, 123) and of *Thuja*. It can be obtained by reduction of thujone or tanacetone, into which it is readily reconverted by oxidation. Both the naturally occurring material and that obtained from thujone are not stereochemically homogeneous, but mixtures of at least two forms. For this reason the physical constants of different samples of thujyl alcohol vary widely (*Paolini* and *Divizia*, Lincei (5) **21**, I, 570). A liquid dextrorotatory form, d^{20} 0·9187, $[\alpha]_D$ + 116·93°, has been obtained from the reduction product of α-thujone by means of the cinchonine salt of the hydrogen phthalate; in a similar manner, the strychnine salt yields a thujyl alcohol, m.p. 28°, $[\alpha]_D^{20}$ — 9·12° (c = 35·98 in toluene). The dextrorotatory thujyl alcohol is oxidised by chromic acid to β-thujone (see below). The methylxanthogenate of the dextrorotatory alcohol yields pure α-thujene (p. 241), whereas that of the laevorotatory alcohol yields, probably, β-thujene (*Tchugaev* and *Fomin*, Ber. **45**, 1293). In the animal organism thujyl alcohol is hydrated to p-menthane-2:4-diol (see below) before combination with glucuronic acid (*Hämalainen*, C. 1912 II, 854; Skand. Arch. Physiol. **27**, 141). For the heat of combustion see *Roth* and *Oestling*, Ber. **46**, 313.

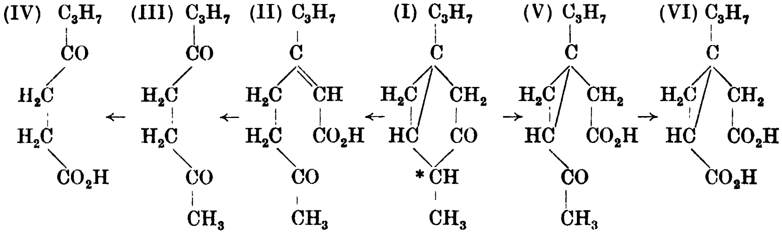
Sabinol, $C_{10}H_{16}O$, 

$$CH_2{=}C\begin{cases}CH(OH)-CH_2\\CH\;-\;-CH_2\end{cases}\!\!\!C{-}C_3H_7$$

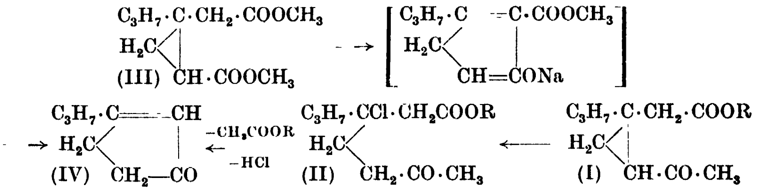
b.p. 208°, d^{15} 0·9518, $[\alpha]_D$ + 7° 56′, n_D^{20} 1·4895, is an unsaturated secondary alcohol which occurs stereochemically pure in the free state and as its acetate in oil of savin, *Oleum sabinae*. *Hydrogen phthalate*, m.p. 94–95°; *strychnine salt of the hydrogen phthalate*, m.p. 200–201° (*Paolini* and *Rebora*, Lincei (5) **25**, II, 377); *p-nitrobenzoate*, m.p. 76°. When heated with zinc dust or aluminium isopropoxide it gives tanacetone (*Schmidt*, Ber. **62**, 103); reduction with Na and alcohol gives thujyl alcohol, and dehydration cymene. Catalytic hydrogenation converts sabinol into thujyl alcohol or thujane, according to the conditions. Sabinol is a very poisonous abortifacient; in the organism it is converted into *sabinolglucuronic acid*, m.p. 82°, the strychnine salt (+ $3H_2O$), m.p. 192–193°, of which is so characteristic that it may be used to detect poisoning with oil of savin (*Hamalainen*, C. 1912 II 855; Skand. Arch. physiol. **27**, 141). Careful oxidation with $KMnO_4$ converts sabinol into **sabinylglycerol,** $C_{10}H_{15}(OH)_3$, m.p. 153°, which is readily dehydrated to cumyl alcohol; energetic oxidation yields α-tanacetone dicarboxylic acid (see below and p. 32); *Fromm*, Ber. **33**, 1191; *Semmler*, ib. 1459; *Wallach*, Ann. **360**, 98; *Hasselstrom*, Ann. Acad. Sci. Fenn. A. **29**, No. 5,3; C. 1927 II 2295). Dilute sulphuric acid brings about fission of the 3-ring, addition of H_2O and migration of the semicyclic double bond into the ring. The unsaturated glycol, $C_{10}H_{16}(OH)_2$, is reduced by Paal's method to *p-menthane-2:4-diol*, m.p. 93–94°; b.p. 135–140°/9 mm.; this is dehydrated to an unsaturated alcohol, $C_{10}H_{17}OH$, which may be converted into carvenone (*Wallach*, Ann. **414**, 201).

3. Amine. — **Thujylamine** $C_{10}H_{17}NH_2$, b.p. 195°, is obtained by reduction of β-thujone oxime. Its *hydrochloride*, m.p. 260–261°, gives isothujene (p. 241) on heating. It has an antiseptic action and hinders secretion (Germ. Pat. 574,654).

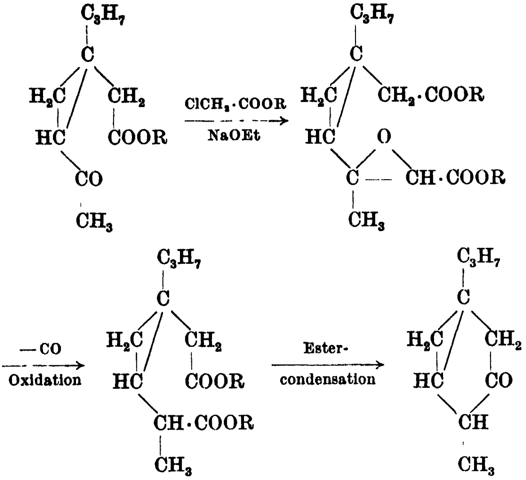
4. Ketones. — **Thujone,** *tanacetone*, $C_{10}H_{16}O$, (I), b.p. 201–202°/760 mm., 103–104°/40 mm., d^{20} 0·9152, n_D^{20} 1·4530 (*Rose* and *Livingstone*, Am. **34**, 201), occurs in nature in two stereoisomeric forms; as laevorotatory α-thujone, $[\alpha]_D$ —10° 23′, *semicarbazone* m.p. 186°, liquid *oxime*, *tetrazole* m.p. 86° (Germ. Pat. 606,615), mainly in thuja oil, and as dextrorotatory β-thujone (tanacetone), $[\alpha]_D$ + 76·16°, *semicarbazone* m.p. 171–173°, *oxime* m.p. 55°, *tetrazole* m.p. 95°, principally in tansy oil from *Tanacetum vulgare*. Mixtures of both forms have been found in wormwood oil, sage oil, absinthe oil and in the oil of various species of *Artemisia* (*Wallach*, Ann. **336**, 247). For its Raman spectrum see *Dulou*, Bull. Pin 2 (1934), 214. Thujone is the strongest and most widely distributed nerve poison ocurring in essential oils. The toxic action of wormwood, which is due to thujone, has lead to the prohibition of absinthe in France and Switzerland. The isomerism of α- and β-thujone, which give identical degradation products, is due to the different arrangement of the H and CH_3 attached to the carbon atom C* (formula I). α- and β-Thujone are reversibly interconvertible under the influence of alkali (*Wallach*, Ann. **408**, 179). The optical antimer of α-thujone can be obtained from the semicarbazone by prolonged heating with phthalic anhydride and water. The α-thujone of $[\alpha]_D + 10^\circ 23'$ so obtained forms a *d,l*-compound with an equal weight of the starting material (*Paolini*, Ann. Chim. appl. **15**, 414). When oxidised with $KMnO_4$, both forms yield the structurally isomeric α- and β-**thuja- or tanacet-ketonic acids,** $CH_3CO{\cdot}C_7H_{12}{\cdot}CO_2H$, m.p. 75° and 78°, respectively, of which the α-acid (V) is saturated, and the β-acid (II) unsaturated (*Roth* and *Oestling*, Ber. **46**, 311). α-Thujaketonic acid (p. 29) is also formed by atmospheric oxidation of thujone and is the cause of the acidity developed by oils containing thujone on long standing. On heating, the α-acid passes into the β-, which yields on oxidation first a diketone (III) and then δδ-dimethyl-laevulinic acid (IV). α-Thujaketonic acid (V) is converted by hypobromite into α-tanacetone-dicarboxylic acid (*α-thujadicarboxylic acid*) (VI) $C_9H_{14}O_4$, m.p. 142°, a saturated dibasic acid which readily forms an anhydride (p. 32); this acid is also obtained by the oxidation of sabinol, sabinene (p. 240) and α-thujene (p. 241). With hypobromite, β-thujaketonic acid gives the unsaturated *β-thujadicarboxylic acid,* m.p. 116–118°, which, on further oxidation, also gives δδ-dimethyllaevulinic acid (IV):



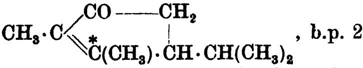
Tanacetophorone (IV, below), a cyclopentenone derivative, b.p. 212–214°, *semicarbazone* m.p. 187–188°, is obtained from α- (I) and β-thujaketonic acid by esterification with alcoholic hydrogen chloride, followed by treatment of the chloro-ester (II) with sodium ethoxide, or from α-tanacetone-dicarboxylic ester (III) directly by treatment with sodium ethoxide (*Wallach*, Ann. **414**, 220; pp. 57, 69):



Condensation of thujone with benzaldehyde gives different products according to the reaction conditions. With two mols. of benzaldehyde a **tetrahydropyrone derivative,** $C_{24}H_{28}O_2$, is formed, which occurs in two forms, m.p. 115° (labile) and 147° (stable) (*Cornubert* and *Borrel*, C. r. **183**, 294). With 1 mol. benzaldehyde **benzylidene-thujone,** $C_{17}H_{20}O$, b.p. 178°/9 mm., is produced; this is oxidised by $KMnO_4$ to benzoic acid and *homotanacetone-dicarboxylic acid,* $C_{10}H_{16}O_4$, m.p. 148°. The latter, like α-tanacetone-dicarboxylic acid (p. 32) and tanacetone itself, contains a cyclopropane ring (*Semmler*, Ber. **36**, 4367; cf. *Fromm*, Ber. **33**, 1192). For the molecular refraction of these compounds see *Oestling*, J. **101**, 457, and for the heat of combustion, *Roth* and *Oestling*, Ber. **46**, 311, 313. A partial synthesis of thujone from α-thujaketonic ester has been carried out (*Ruzicka* and *Koolhaas*, Helv. **15**, 944):



On heating with sulphur, α-thujone yields carvacrol (*Takagi* and *Tamaka*, C. 1926 I 80). In the organism it is converted into the glucuronic acid compound of p-menthane-2-one-4-ol, which on hydrolysis yields carvenone (p. 234) formed from this keto-alcohol by dehydration (*Hamalainen*, Skand. Arch. Physiol. **27**, 141). Alcoholic sulphuric acid converts thujone into isothujone, whereas heating to 280° yields carvotanacetone. These two ketones are unsaturated, in contradistinction to β-thujone (*Wallach*, Ber. **28**, 1959). *β-Thujone oxime*, m.p. 54–55°, is converted by alcoholic sulphuric acid into carvacrylamine or into isothujone oxime (*Tiemann*, Ber. **30**, 325); treatment with PCl_5 yields the lactam, *thujone isoxime*, m.p. 90° (*Wallach*, Ann. **336**, 270).

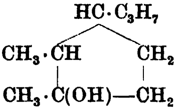
Isothujone, 

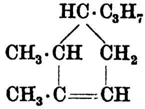
$$CH_3\cdot \overset{*}{C}\left\langle\begin{matrix}CO-CH_2\\ C(CH_3)\cdot CH\cdot CH(CH_3)_2\end{matrix}\right.$$

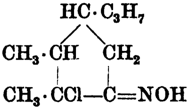
, b.p. 231°, d 0·927, n_D 1·4822, inactive, is obtained from thujone and sabinol by rearrangement; α- and *β-semicarbazones*, m.ps. 208° and 148°, *oxime*, m.p. 119–120°, *benzylidene-isothujone* $(C_{10}H_{14}O):CH\cdot C_6H_5$, m.p. 83°. On oxidation, isothujone gives a keto-lactone $C_{10}H_{16}O_3$, and finally, β-isopropyl-laevulinic acid $CH_3\cdot CO\cdot CH(C_3H_7)\cdot CH_2\cdot COOH$. On reduction a saturated alcohol, **α-thujamenthol,** *dihydro-isothujol* $C_{10}H_{19}OH$, b.p. 212°, d^{18} 0·899, n_D 1·4611, is obtained; this is oxidised by chromic acid to **α-thujamenthone,** $C_{10}H_{18}O$, b.p. 208°, d^{18} 0·8915, n_D 1·4474, *semicarbazone* m.p. 185°, *oxime* m.p. 95°, *isoxime* m.p. 117°. By reduction of isothujone, or thujone itself, by the Sabatier-Senderens method at 175–180° α-thujamenthone is produced (*Godchot*, C. r. **158**, 1807). Reduction of isothujone by the Paal-Skita method yields **β-thujamenthone,** which can be reconverted into isothujone, but not into α-thujamenthone, just as α-thujamenthone cannot be converted into β-thujamenthone. It appears from these facts that the isomerism involved is concerned, not with the C-atom next to the CO-group as with the thujones, but with the more distant C* atom. β-Thujamenthone has b.p. 215–216·5°, d^{19} 0·8990, n_D 1·4511, *semicarbazone* m.p. 190–191°, *oxime* m.p. 130–131°, *isoxime* m.p. 102° (*Wallach*, Ann. **408**, 163). Reduction of β-thujamenthone with sodium gives **β-thujamenthol,** b.p. 216·5–217·5°, d^{19} 0·8995, n_D 1·4583 (*Wallach*, Ann. **323**, 348; **336**, 276; Ber. **28**, 1958). Oxidation of α- and β-thujamenthone gives the same *α-methyl-β-isopropyl-glutaric acid,* m.p. 137–138° (*Wallach,* Ann. **408**, 182).

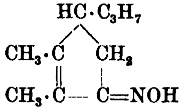
Reduction of α-thujamenthone oxime with sodium and alcohol yields **α-thujamenthylamine,** b.p. 196–197°, *hydrochloride* m.p. 187°, *acetyl derivative* m.p. 129–130°. This amine reacts normally with nitrous acid to give α-thujamenthol together with some hydrocarbon. On the other hand, the same reaction with **β-thujamenthylamine,** b.p. 206·5°, *hydrochloride* m.p. above 230°, *acetyl derivative* m.p. 96°, yields tert.-thujamenthol (see below).

On dehydration α- and β-thujamenthol yield, respectively, **α-thujamenthene,** $C_{10}H_{18}$, b.p. 163–165°, d^{22} 0·8085, n_D 1·4503, and **β-thujamenthene,** b.p. 161–164°, $d^{18\cdot5}$ 0·8100, n_D 1·4514. Neither of these gives any solid derivative; such derivatives can, however, be obtained from the **thujamenthene** (II), b.p. 164–166°, d^{21} 0·8100, n_D 1·4460, derived from **tert.-thujamenthol** (I). This thujamenthene readily gives a *nitrosochloride* (III), m.p. 108°, which may be converted into isothujone oxime (IV), m.p. 119–120°:

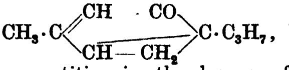
(I) 

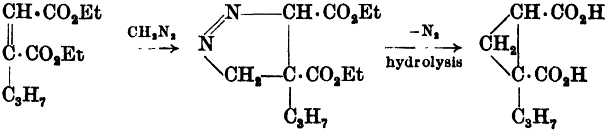
(II) 

(III) 

(IV) 

For 1 : 2-dimethyl-3-isopropyl-cyclopentane see *Richter, Wolff* and *Presting* (Ber. **64,** 875).

Umbellulone, $C_{10}H_{14}O$,  $CH_3\cdot C\begin{array}{l}\diagup CH\cdot CO\diagdown\\ \diagdown CH-CH_2\diagup\end{array}C\cdot C_3H_7$, b.p. 93°/10 mm., $[\alpha]_D$ — 37°, occurs in large quantities in the leaves of the Californian laurel, *Umbellularia californica* (*Drake* and *Stuhr*, J. Am. pharm. Ass. **24** (1935), 196); *semicarbazone*, m.p. 242°. It rearranges to thymol when heated to 280° (U.S.A. Pat. 1,666,342, 1,967,440). Bromination, followed by distillation, yields some p-cymene together with other products which contain bromine. Reduction with sodium and alcohol yields the saturated alcohol, *dihydro-umbellulol,* $C_{10}H_{17}\cdot OH$, m.p. 55–56°, b.p. 90°/10 mm., which is oxidised by chromic acid to *dihydro-umbellulone,* $C_{10}H_{16}O$, b.p. 85°/10 mm. (*semicarbazone* m.p. 158–159°; *oxime* m.p. 72°). The latter is also produced from umbellulone by hydrogenation under mild conditions, whereas energetic hydrogenation gives a monocyclic alcohol, $C_{10}H_{20}O$, which is probably 1 : 2-dimethyl-3-isopropylcyclopentane-4-ol (*Wienhaus* and *Todenhofer,* Schimmel Ber., Jubil.-Ausg. **1929,** 283). Oxidation of the benzylidene derivative of dihydroumbellulone with $KMnO_4$ gives homotanacetone-dicarboxylic acid (p. 33), as with benzylidene-thujone (p. 243). Oxidative degradation of umbellulone (*Tutin,* J. **89,** 1104) gives *umbellularic acid* (I), m.p. 78° (+ $1H_2O$), $[\alpha]_D$ — 89·7° (p. 31), which has been synthesised as follows (*Rydon,* J. **1936,** 829):



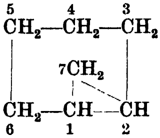
(I).

CARANE, PINANE AND CAMPHANE GROUPS

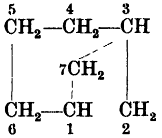
As has been pointed out on p. 239, the members of these groups contain a cyclohexane ring in which two carbon atoms in the o-, m- or p-positions are joined together by means of the central carbon atom of an isopropyl group. Representatives of all three groups, with o-, m- or p-carbon bridges, occur in nature. An o-bridge is present in the carenes, whose carbon skeleton is more appropriately classified as a condensed ring system (p. 150); pinene, an extraordinarily widely distributed terpene, belongs to the group with a m-bridge, while the p-bridge group includes camphor, the most important member of this class, and fenchone closely related to it, as well as the terpenes derived from them, camphene and the fenchenes, which have been prepared artificially.

A characteristic behaviour of the members of this group is the remarkable ease with which they undergo intramolecular rearrangement, especially with acid reagents; such rearrangement causes a complete change in the ring system and has made the correlation of degradation products and the determination of their constitution a problem of extreme difficulty.

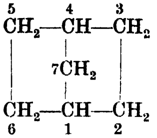
Nomenclature. — In general, the names used are derived from those of the species of plants in which some of the more important compounds occur. Only in certain cases is a systematic nomenclature of value; in these cases reference is made to the completely demethylated hydrocarbons of the three main groups of which the first and last are known; these are called norcarane, norpinane and norcamphane, and the carbon atoms are numbered as shown below (see also *Bredt* and *Savelsberg*, J. pr. **97**, 1; cf. p. 180):



Norcarane



Norpinane



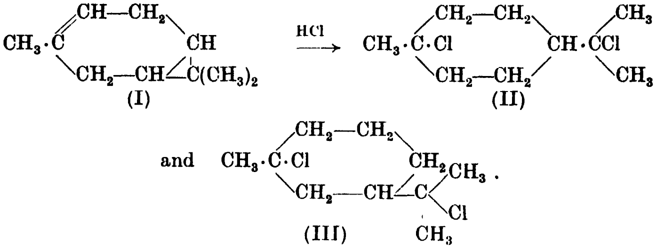
Norcamphane

II. CARANE GROUP

The compounds of this group resemble those of the sabinane group in containing a cyclopropane ring, which is, however, combined with a cyclohexane ring. Hydrocarbons of this series occur in essential oils; the other compounds have only been prepared artificially.

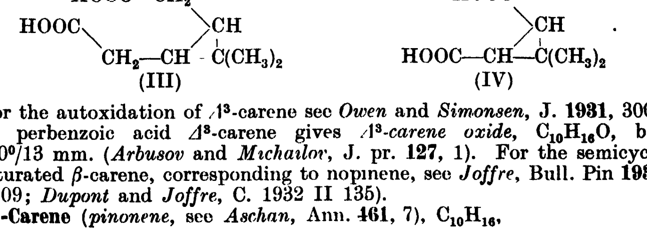
The parent hydrocarbon, **norcarane** (see formula above), b.p. 111–112°, has been obtained by the decomposition of the barium salt of norcaranecarboxylic acid (from cyclohexene and diazoacetic ester) (*Ebel*, *Brunner* and *Mangelli*, Helv. **12**, 19; cf. p. 165).

1. Hydrocarbons. — **Δ^3-Carene** (*isodiprene*; see *Aschan*, Ann. **461**, 4), $C_{10}H_{16}$ (I), b.p. 168–169°/705 mm., n_D^{20} 1·469, d_{30}^{30} 0·8586, occurs as the *d*-form in Indian turpentine oil from *Pinus longifolia* Roxb., in Sumatra turpentine oil, in Swedish pine-needle oil, in pine-root oil, in knee-pine oil from *Pinus pumilio*, in German gum turpentine oil (*Stephan*, J. pr. **143**, 123) and in many other oils; the *l*-form occurs in the oil of *Kaempferia galanga*. In some of these oils, e.g. Swedish pine-needle oil, sylvestrene (p. 213) was formerly believed to be present, owing to the formation of sylvestrene dihydrochloride by the action of hydrogen chloride. It has, however, been shown (*Simonsen* et al., J. **117**, 570; **123**, 549; **1928**, 359; **1929**, 305) that sylvestrene does not occur if the oil is carefully separated, but only arises as a product of secondary change of the Δ^3- and Δ^4-carene present, by heat (in kiln turpentine oil) or chemical reagents (in sulphate turpentine oil). Only after such treatment does the oil give the blue colour with acetic anhydride and a drop of sulphuric acid which is characteristic of sylvestrene (*Wallach*, Ann. **239**, 24; *Semmler* and *von Schiller*, Ber. **60**, 1591). Δ^3-Carene is a colourless oil with a characteristic sweet odour. It forms a crystalline *nitrosate*, decomp. 147°, and a *nitrosochloride*, m.p. 101–102° (*Lagache*, C. 1928 I 339), which with Na_2CO_3 in alcohol gives *nitroso-Δ^3-carene*, m.p. 89–90°, and with aniline, *Δ^3-carenenitrolanilide*, m.p. 143–144°. Dilute sulphuric acid does not bring about hydration of Δ^3-carene, but hydrochloric acid in acetic acid solution decomposes it and gives a mixture of sylvestrene dihydrochloride (III), m.p. 72°, and dipentene dihydrochloride (II), m.p. 48–50°:



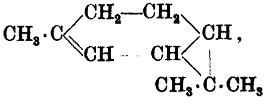
(I) (II) (III)

Treatment of Δ^3-carene with $KMnO_4$ gives as primary products two glycols, m.ps. 68–70° and 90–91°, which are apparently stereoisomeric. Further treatment gives, according to experimental conditions, the following acids: dimethylmalonic, as-dimethylsuccinic, cis- and trans-caronic, (decomposition points 174–175° and 213°; p. 31), cis-homocaronic, $C_8H_{12}O_4$, m.p. 137° (p. 32) (*Hariharan, Menon* and *Simonsen*, J. **1928**, 431), and a hydroxy-acid $C_{10}H_{16}O_5$ in two forms of m.p. 133° and 192°, which is probably the oxidation product of the enolic form of a ketonic acid formed in the oxidation (*Simonsen* and *Rao*, J. **123**, 549; cf. *Wallach*, Ann. **362**, 263). The oxidation of Δ^3-carene with ozone (*Semmler* and *von Schiller*, Ber. **60**, 1591) gives the keto-aldehyde $C_{10}H_{16}O_2$ (I) (*disemicarbazone*, m.p. decomp. 198–199°), which on cautious oxidation gives the ketonic acid $C_{10}H_{16}O_3$ (II) (*semicarbazone* m.p. 182–183°). Further degradation of this acid with alkaline hypobromite gives a dicarboxylic acid $C_9H_{14}O_4$ (III), m.p. 112–113°, while acid permanganate leads to cis-caronic acid (IV), m.p. 174–175°:

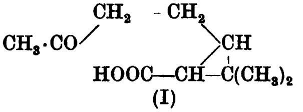

(I) (II) (III) (IV)

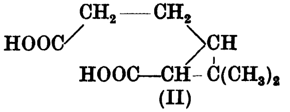
For the autoxidation of Δ^3-carene see *Owen* and *Simonsen*, J. **1931**, 3001. With perbenzoic acid Δ^3-carene gives *Δ^3-carene oxide*, $C_{10}H_{16}O$, b.p. 79–80°/13 mm. (*Arbusov* and *Michailov*, J. pr. **127**, 1). For the semicyclic unsaturated β-carene, corresponding to nopinene, see *Joffre*, Bull. Pin **1931**, 79, 109; *Dupont* and *Joffre*, C. 1932 II 135).

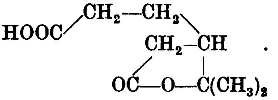
Δ^4-Carene (*pinonene*, see *Aschan*, Ann. **461**, 7), $C_{10}H_{16}$,

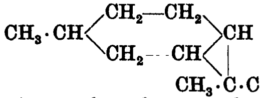


occurs as its *d*-form, together with Δ^3-carene, in the oil from *Andropogon iwarancusa* (*Simonsen*, J. **121**, 2292), and in pine-root oil (*Semmler* and *von Schiller*, Ber. **60**, 1591); b.p. 165·5–167°/707 mm., d_{30}^{30} 0·8525, n_D^{30} 1·474. On treatment with hydrogen chloride in acetic acid it gives, like Δ^3-carene, dipentene dihydrochloride and sylvestrene dihydrochloride. Cautious oxidation with $KMnO_4$ gives *d*,1:1-dimethyl-2-γ-ketobutyl-cyclopropane-3-carboxylic acid (I) (p. 29), *semicarbazone* m.p. 182–183° (synthesis of the *d,l*-compound, see *Owen* and *Simonsen*, J. **1932**, 1424). With sodium hypobromite this ketonic acid gives the dicarboxylic acid $C_9H_{14}O_4$ (II), m.p. 104–105° (p. 32), and from this by the action of HBr at 100° homoterpenylic acid (III) m.p. 98–100° is obtained (p. 255):

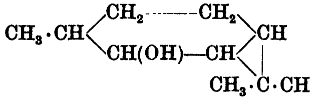

(I)


(II)


(III)

Carane, $C_{10}H_{18}$, , can be prepared from carone hydrazone by heating with sodium methoxide (*Semmler* and *Feldstein*, Ber. **47**, 387); b.p. 92–93°/10 mm., and 165–166° at atmospheric pressure with slight rearrangement (probably to Δ^3-menthene), d_{20}^{20} 0·8381, n_D 1·4582. After treatment with hydrogen in the presence of Pt-black its physical constants are unchanged (*Krestinski* and *Ssolodki*, J. pr. **126**, 14; *Zelinsky* and *Levina*, Ann. **476**, 62), but it can be dehydrogenated with Pd-asbestos to a mixture of p-menthane and cymene (*Levina*, C. 1935 II 3650).

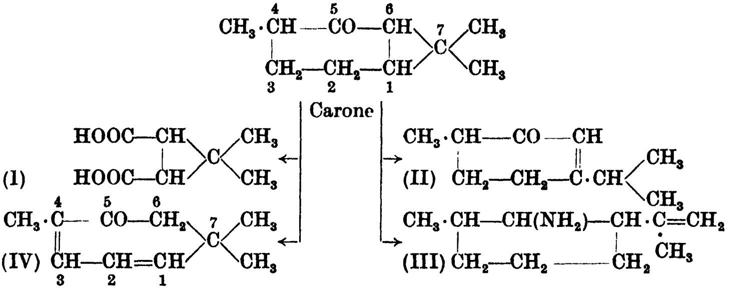
2. Alcohols. — **Carol,** $C_{10}H_{18}O$ (*Menon* and *Simonsen*, C. 1927 II 1473),


,

is obtained as its *l*-form by treating *d*-carylamine (see below) with nitrous acid; b.p. 141–142°/100 mm.; it is an oil with a pleasant smell resembling that of linalool. For an isomer of carol see *Semmler* and *von Schiller*, Ber. **60**, 1591; for hydroxy-chloro-carane, $C_{10}H_{17}OCl$, see *Pillay* and *Simonsen*, J. **1928**, 359.

3. Ketones. — **Carone,** $C_{10}H_{16}O$, (formula below), b.p. 98°/13 mm., d_4^{17} 0·955, n_D^{16} 1·478, $[\alpha]_D$ + 134° (*Richter*, *Wolff* and *Presting*, Ber. **64**, 877); is obtained from dihydrocarvone hydrochloride or hydrobromide by the action of alcoholic potash. It is relatively stable to permanganate, which only attacks it at 100° and oxidises it to caronic acid (1 : 1-dimethyl-2 : 3-cyclopropane-dicarboxylic acid) (I) (p. 31). The cyclopropane ring of carone can be opened in three different directions: (a) at the C_6—C_7 bond: on heating to about 210° carone rearranges to carvenone (II) (*Brühl*, Ber. **32**, 1222); by the action of HBr it is reconverted into dihydrocarvone hydrobromide, and sulphuric acid gives hydroxy-tetrahydrocarvone: (b) at the C_1—C_7 bond: carylamine, obtained by the reduction of *carone oxime*, m.p. 78°, is stable to permanganate, but rearranges with HCl to the isomeric unsaturated vestrylamine (III), the hydrochloride of which gives carvestrene on heating

(*Baeyer*, Ber. **27**, 3486): (c) at the C_1—C_6 bond: **cyanocarone,** $C_{10}H_{15}(CN)O$, m.p. 55°, obtained by the action of alcoholic potash on cyanodihydrocarvone hydrobromide, can be degraded to caronic acid, but on warming with caustic potash gives eucarvone (IV) (see below) (*Clarke* and *Lapworth*, J. **97**, 11).



Carone semicarbazone: active m.p. 167–169°, *dl*, m.p. 178°. *Carone oxime*: active, a liquid, *dl*, m.p. 77–79°. *Bisnitrosocarone*: active, m.p. 116–118°, *dl*, m.p. 148°.

For **carenone** $C_{10}H_{14}O$, *semicarbazone* m.p. 159–161°, a by-product in the permanganate oxidation of Δ^3-carene, and the corresponding saturated ketone, *semicarbazone* m.p. 223–224°, isomeric with carone, see *Semmler* and *von Schiller*, Ber. **60**, 1591.

A **hydroxy-carone,** $C_{10}H_{16}O_2$, b.p. 135°/19 mm., can be obtained from dihydrocarvone dibromide; with caustic soda this gives hydroxy-bromtetrahydrocarone, which by treatment with methyl alcoholic potash is transformed into hydroxy-carone. If this is treated with dilute sulphuric acid, it is changed into a ketoderivative of terpin (*Baeyer*, Ber. **31**, 3208).

Pseudo-phenylacetic acid or nor-caradiene-carboxylic acid (pp. 73 and 165), prepared from benzene and diazoacetic ester, has a similar constitution and undergoes changes analogous to those of carone.

Eucarvone (IV, above), b.p. 88°/10 mm., d_4^{20} 0·9490$_D^{20}$, n 1·50872 (*Auwers*, Ann. **415**, 164), has a 7-membered ring, but is treated here because of its relationship to carone. It is formed from carvone hydrobromide with alcoholic potash, evidently with the intermediate formation of an unstable $\alpha\beta$-unsaturated carone (cf. the transformation of cyano-carone into eucarvone). It is optically inactive, and gives a deep blue unstable colour when evaporated with methyl alcoholic potash. *Semicarbazone* m.p. 184°; *oxime* m.p. 106°; *hydroxylamino-oxime* m.p. 142° (*Harries*, Ann. **330**, 275). It condenses with benzaldehyde to give *benzylidene-eucarvone*, m.p. 113°. Oxidation leads to acetic and as-dimethylsuccinic acids. Autoxidation of eucarvone: p. 73 and 153. *Adduct* with *maleic anhydride*: *Alder* and *Stein*, Ann. **515**, 167.

On continued heating eucarvone rearranges to carvacrol; similarly 2-chlorcymene is formed by the action of PCl_5. The unsaturated diamine obtained by reduction of the hydroxylamino-oxime of eucarvone gives p-cymene when its phosphate is distilled. In these cases it is assumed that cycloheptatriene derivatives are formed intermediately, and that these rearrange under the conditions of reaction to the more stable benzene derivatives (cf. the transformation of cycloheptatriene into benzyl bromide, p. 71).

Two series of dihydro-eucarvyl derivatives are known. **α-Dihydro-eucarveol,** $C_{10}H_{17}OH$, b.p. 114°/16 mm., is obtained together with tetrahydroeucarveol by the reduction of eucarvone with sodium and alcohol; on oxidation it gives **α-dihydro-eucarvone,** $C_{10}H_{16}O$, b.p. 87°/16 mm. (*Wallach*, Ann. **339**, 102); *semicarbazone* m.p. 189–191°. **α-Dihydro-eucarvylamine,** $C_{10}H_{17}NH_2$, b.p. 117°/40 mm., from eucarvoxime with sodium and alcohol; its hydrochloride gives euterpene on heating (*Wallach*, Ann. **305**, 239). The compounds of the α-series have the double bond either in the 1: 2- or 2: 3 position (see formula IV, p. 249).

The compounds of the β-series are obtained by partial reduction of eucarvoxime with palladium and hydrogen (*Wallach*, Ann. **403**, 73) to *β-dihydro-eucarvoxime* m.p. 122–123°, from which **β-dihydro-eucarvone,** $C_{10}H_{16}O$, b.p. 213–214°, can be obtained; since this can be degraded to ββ-dimethyladipic acid it is a $\Delta^{3\cdot4}$ compound. This formula is also supported by the fact that β-dihydro-eucarvoxime can be reduced directly with sodium and alcohol to **tetrahydro-eucarvylamine,** $C_{10}H_{19}NH_2$, b.p. 208·5° (*Wallach*, Ann. 414, 367). The dihydro-compounds of the α-series and those of the β-series give the same tetrahydro-derivatives on further reduction. From β-dihydro-eucarvone a *dibromide* $C_{10}H_{16}OBr_2$, m.p. 71–72°, can be prepared, from which by the action of caustic potash α-cyclogeranic acid $C_{10}H_{16}O_2$ is obtained together with products of uncertain constitution (*Wallach*, Ann. **418**, 53).

Tetrahydro-eucarvone, $C_{10}H_{18}O$, b.p. 208–209°, d^{18} 0·9095, n_D 1·4568, a substance smelling like menthone, can be prepared from eucarvone by reduction by the Paal-Skita method, by hydrolysis of tetrahydroeucarvoxime, m.p. 56–57°, prepared from eucarvoxime with Pd and hydrogen (*Wallach*, Ann. **403**, 87), and from tetrahydro-eucarveol (see below) by oxidation. With bromine it forms a *monobromide* m.p. 32° or a *dibromide* m.p. 68°, according to the experimental conditions (*Wallach*, Ann. **414**, 367; **418**, 53).

Tetrahydro-eucarveol, $C_{10}H_{20}O$, b.p. 216°, can be obtained from tetrahydro-eucarvone by reduction with sodium and alcohol, or from the dihydro-carveols with Pd and hydrogen; it is also prepared from eucarvone by treatment with sodium and alcohol, together with α-dihydrocarveol. *Phenyl-urethane* m.p. 74–75°.

III. PINANE GROUP.

While carone and its important degradation product, caronic acid, can be synthesised relatively easily, a complete synthesis of α- and β-pinene has not yet been carried out. The artificial preparation of norpinic acid, 2:2-dimethyl-cyclobutane-1:3-dicarboxylic acid (p. 39), which is the final product of the oxidative degradation of pinene (p. 253), has been achieved; from this, pinononic acid has been prepared, which can give keto-norpinone (*Guha* and *Ganapathi*, Ber. **69**, 1185). Further, pinononic acid can be used for the synthesis of iso-homocamphoric acid, the lead salt of which on distillation furnishes *dl*-verbanone, and this has led to a complete synthesis of *dl*-δ-pinene and *dl*-pinane (*Komppa* and *Klamia*, Ber. **70**, 788). A partial synthesis of α-pinene has been carried out from pinonic acid (*Ruzicka*, Helv. **3**, 765; **4**, 666; **7**, 489), but there is still a gap in the complete synthesis between verbanone and α- or β-pinene.

1. Hydrocarbons. — The fundamental hydrocarbon, **norpinane,** bicyclo-[1:3:3]-heptane (p. 246) is not yet known.

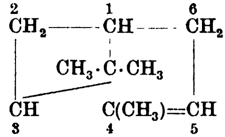
α- and β-Pinene. — The pinenes, chiefly α-pinene, are widely distributed in essential oils and are the chief constituents of oil of turpentine, the essential oil obtained from the oleoresins of various conifers, notably of the various species of *Pinus*.

Turpentine Oil. — The resinous secretion from the conifers, called turpentine, consists of a solution of resins in turpentine oil, which can be distilled off in steam, leaving the resin colophony. Turpentine oil is a colourless liquid, d 0·856–0·87, b.p. 155–165°; its persistent smell arises from the peroxides formed in it by autoxidation in air (see below). It is almost insoluble in water, but is miscible with absolute alcohol and ether. It dissolves sulphur, phosphorus and rubber and is used for the preparation of varnishes and oil-colours. Turpentine oil is used in medicine as an antiseptic and a stimulant, e.g. *terpichine* (10–20% solution of pure turpentine oil in olive oil with the addition of 0·5% of quinine and 0·5% of anaesthesin), etc.

Turpentine oils vary according to their source, and particularly in optical rotation. The American, Algerian and Greek turpentine oils contain chiefly *d*,α-pinene, the French and Spanish chiefly *l*,α-pinene. α-Pinene is also found as the *d*-, the *l*- and the *dl*-forms in many other essential oils, such as those of eucalyptus, juniper berry, and sage.

In most cases, and particularly in turpentine oils, α-pinene is accompanied by small amounts of a closely related higher-boiling terpene with a semicyclic double bond known as β-pinene, which gives the same hydrochloride with HCl; its oxidation products, however, are characteristically different. The names γ- and δ-pinene were given to two ring-unsaturated pinene derivatives. γ-Pinene was thought to have a double bond in the 3:4-position (*Wallach* and *Blumann*, C. 1907 II 983), but this is sterically impossible (cf. pp. 183 and 270); the compound does not exist and the name should not be used. δ-Pinene, however, with the double bond in the sterically possible position 5:6-, has been synthesised (see below).

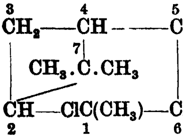
α-Pinene, $C_{10}H_{16}$

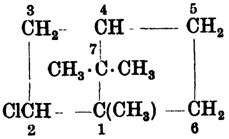


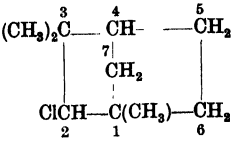
b.p. 155°, d^{20} 0·8592, n^{21}_D 1·4664; parachor: *Kurssanov*, C. 1935 II 3494; electric moment: *Svirbly*, *Ablard* and *Warner*, Am. **57**, 652; Raman spectrum: *Nevgi* and *Jakkar*, C. 1935 II 204. *d*,α-Pinene is obtained by fractional distillation of American or Greek turpentine oils, *l*,α-pinene from French turpentine oils, but neither is optically pure. The highest observed rotations are for *d*, α-pinene from Port Orford cedar oil: $[\alpha]_D + 51{\cdot}52°$ (*Schorger*, C. 1914 II 1107; *Gabiano*, C. r. **199**, 1607); for *l*,α-pinene from the gum of the Douglas pine: $[\alpha]_D - 51{\cdot}28°$ (*Thurber* and *Thielke*, Am. **53**, 1030). α-Pinene is obtained very easily from its nitrosochloride (p. 255) by treatment with aniline or with sodium acetate in acetic acid, also by the action of sodium ethoxide on verbenone hydrazone and by reduction of verbenene with sodium and alcohol. The hydrocarbon $C_{10}H_{16}$ obtained by thermal decomposition of pinocamphyl-trimethylammonium hydroxide (*Ruzicka* and *Trebler*, Helv. **3**, 756) or of pinocamphylxanthogenic methyl ester (*Tchugaev*, C. 1908 I 1179) is a mixture of α-pinene and δ-pinene, as is shown by the fact that pinocamphoric acid and pinonic acid are the products of its oxidation (*Ruzicka* and *Pontalti*, Helv. **7**, 489).

α-Pinene contains a double bond in the ring, as can be shown, for example, by treatment with diazoacetic ester (*Buchner* and *Rehorst*, Ber. **46**, 2680). The true halogen addition products of pinene, $C_{10}H_{16}Hal_2$, cannot be isolated, because they immediately undergo further change with rearrangement or rupture of the carbon bridge; substitution also takes place as well as addition. The action of chlorine gives a complex mixture of products from which can be isolated **pinene dichloride,** which is a 2:6-dichlorcamphane (p. 274), m.p. 173–174° (*Aschan*, Ber. **61**, 38) and from which tricyclene can be obtained by removal of chlorine (p. 275), together with pinene hydrochloride, liquid chlorinated products and polychlor-compounds. Similarly with bromine, **pinene dibromide,** i.e. 2:6-dibromcamphane, is obtained with pinene hydrobromide and liquid brominated products (*Pariselle*, C. r. **172**, 1496). By the action of moist hydrogen halides α-pinene gives dipentene dihydrohalides, while with dry hydrogen halides in the cold monohydrohalides are obtained. Under suitable conditions it is possible to isolate the primary addition product of HCl and pinene, "true pinene hydrochloride", which can only be kept unchanged for a short time in ethereal solution (*Meerwein* and *van Emster*, Ber. **55**, 2521; *Meerwein* and *Vorster*, J. pr. **147**, 83).

The change which the "true pinene hydrochloride" (I) undergoes leads chiefly to **bornyl chloride** (II); but some fenchyl chloride (III) is also formed (*Délépine* and *Cachat*, Bull. **39** [1926], 1745). For the transformation of pinene into borneol with the aid of phosphoboric acid, see Germ. Pat. 382,043.


(I)


(II)


(III)

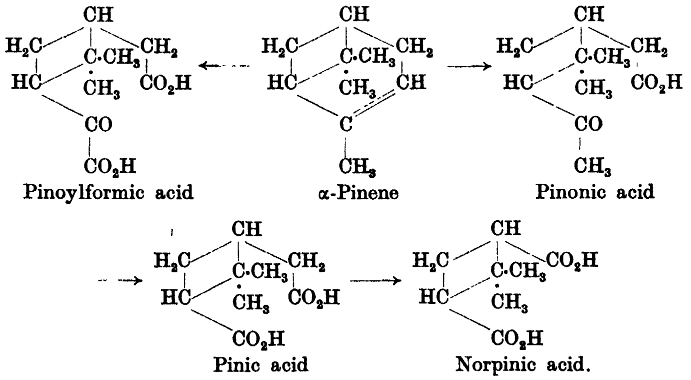
In the same way, when pinene is treated with organic acids, such as acetic, oxalic, trichloracetic, salicylic, tetrachlorphthalic, etc., esters of **borneol** or of the stereoisomeric **isoborneol** (e.g. *Schmidt*, C. 1935 II 2881) are formed, together with varying quantities of the corresponding ester of **fenchyl alcohol** (*Délépine* and *Adida*, Bull. **39** [1926], 782) and other rearrangement products such as camphene, limonene and dipentene. This change from pinene to borneol or isoborneol is made use of technically in the preparation of camphor from turpentine oil (p. 286). In the addition of hypochlorous acid to pinene both the double bond and the four-membered ring disappear. The dichlorhydrins so formed are derivatives of menthane, and with alkali they give pinol oxide, sobrerythritol, pinol chlorhydrin (p. 260) and other compounds (*Wagner* and *Slavinski*, Ber. **32**, 2064; *Henderson* and *Marsh*, J. **119**, 1492). By the action of dilute nitric or sulphuric acid on pinene **terpin hydrate** is formed, while with sulphuric acid in acetic acid or with benzenesulphonic acid (*Earl* and *Kenner*, J. **1927**, 1269) the primary product of hydration and bridge-opening, **α-terpineol** (p. 223), can be isolated. Pinene rearranges to **dipentene** when heated to 250–270°. The change from pinene to **camphene** by heating with organic acids such as formic (*Reismann*, Bull. **41** [1927] 94), abietic (*Peufaillit* and *Austerweil*, French Pat. 563,208), etc., depends apparently on the decomposition of the bornyl or isobornyl esters first formed into camphene and the acid. The catalytic change from pinene to camphene can be carried out with phosphomolybdic and phosphotungstic acids and with other inorganic and inorganic-organic complex acids which give more or less unstable addition compounds with terpenes, and also with salts such as $MgSO_4, H_2O$ or $NiSO_4, H_2O$ (*Schering-Kahlbaum A.-G.*, Brit. Pat. 375,395; Germ. Pat. 570,957, 578,569; Brit. Pat. 391,073; Germ. Pat. 584,165, 597,258; *Tishtchenko* and *Rudokov*, C. 1935 I 2540). When the vapour of pinene is passed over a catalyst at 300–400° (Cr-Cu catalyst of Adkins, "suprax" glass fragments), the bridge opens and isomeric change takes place to monocyclic compounds (dipentene, pyronene [*Dupont* and *Dulou*, C. r. **201**, 219; **202**, 1861]). About 25 % of *allo-ocimene* $(CH_3)_2C{:}CH{\cdot}CH{:}CH{\cdot}C(CH_3){:}CH{\cdot}CH_3$, b.p. 81°/12 mm., 193·5–194·5°/760 mm., d_0^{15} 0·8162, n_D^{15} 1·5448, is also formed by opening of both the bridge and the ring; this compound has been synthesised from the condensation product of methylheptadienone and α-bromopropionic ester by hydrolysis and distillation (*Fischer* and *Löwenberg*, Ber. **66**, 669). *Addition product* with *maleic anhydride*, m.p. 81–82°, with *α-naphthaquinone*, m.p. 122° (*Arbusov*, Ber. **67**, 563, 569; **68**, 1435; C. 1936 II 3681; see also p. 201).

The oxidation products of pinene have been thoroughly investigated. Even in air turpentine oil slowly absorbs oxygen, and the first products of this autoxidation are an unsaturated alcohol, verbenol (p. 258), and the corresponding ketone, verbenone (p. 261). Their formation can be accelerated by the use of oxidation catalysts, e.g. colloidal osmium (*Wienhaus* and *Schumm*, Ann. **439**, 20; *Suzuki*, C. 1935 II 526). Besides these two substances, which still belong to the pinane group, formic and acetic acids and small quantities of cymene are formed, with large amounts of resinous acid substances. For the formation of pinol hydrate from pinene in air under the influence of sunlight see p. 259. Energetic oxidising agents such as nitric acid give terebic acid (p. 254), p-toluic acid, terephthalic acid and other compounds. With chromic acid the chief product is terpenylic acid (p. 255). By oxidation with mercuric acetate, *dl*-sobrerol is formed, a reaction which can be used as a test for pinene, because of the ease with which the sobrerol can be isolated. Sobrerol can be further oxidised to hydroxy-dihydrocarvone or carvone hydrate (p. 238). From the latter, carvone and carvacrol are formed by dehydration with oxalic acid, and terpenylic acid (p. 255) by further oxidation with $KMnO_4$ (*Henderson* and *Agnew*, J. **95**, 289). From pinene and benzoyl peroxide, *pinene oxide* $C_{10}H_{16}O$ is obtained, b.p. 70–71°/12 mm., d_4^{20} 0·9627, n_D^{16} 1·4709 (*Ritter* and *Russell*, Am. **58**, 291), which is also converted into pinol by hydration (*Nametkin* and *Jarzeva*, C. 1925 II 715), but rearranges with $ZnBr_2$ in benzene to campholenaldehyde (*Arbusov*, Ber. **68**, 1430).

Cautious oxidation of pinene with $KMnO_4$ gives first of all **α-pinene glycol,** $C_{10}H_{16}(OH)_2$, b.p. 146°/14 mm. (*Wagner*, Ber. **27**, 2270; cf. also *Slavinski* and *Zacharevicz*, C. 1935 I 3291), which is readily oxidised further to a keto-monobasic acid, **pinonic acid,** $C_{10}H_{16}O_3$, m.p. (active) 70°, (*dl*) 104°, b.p. 168°/12 mm.; *semicarbazone* m.p. (active) 203–204°, (*dl*) 206–207°; *oxime* m.p. (active) 128° and 191°, (*dl*) 150° (*Dupont* and *Brus*, Ann. chim. (9), **19**, 186). A small quantity of a keto-dibasic acid, **pinoylformic acid,** $C_{10}H_{14}O_5$, m.p. (*dl*) 79°, is also formed. α-Pinene ozonide, formed by the action of ozone on pinene (*Harries* and *Seitz*, Ann. **410**, 21), gives pinonic aldehyde from which pinonic acid (*Harries* and *Neresheimer*, Ber. **41**, 38) can also be obtained (*Harries* and *von Splawa-Neyman*, C. 1916 II 994). Pinonic acid is often used as a test for α-pinene in essential oils, particularly when the hydrocarbon is present in a very active form (p. 255, pinene nitrosochloride). For the use of pinonic acid as starting material for the synthesis of pinocamphone see p. 262.

Pinonic acid is easily attacked by oxidation with bromine and alkali or with dilute nitric acid to give the very stable **pinic acid,** $C_9H_{14}O_4$, m.p. 102°, and oxidation of α-hydroxypinic acid, prepared via α-bromopinic acid, furnishes **norpinic acid,** $C_8H_{12}O_4$, m.p. (cis) 174°, (trans) 146°. All these acids contain the 1:1-dimethyl-cyclobutane ("piceane") ring of pinene (*Baeyer*, Ber. **29**, 2776; *Oestling*, J. **101**, 457; C. 1921 I 619). For a synthesis of trans norpinic acid see p. 39.

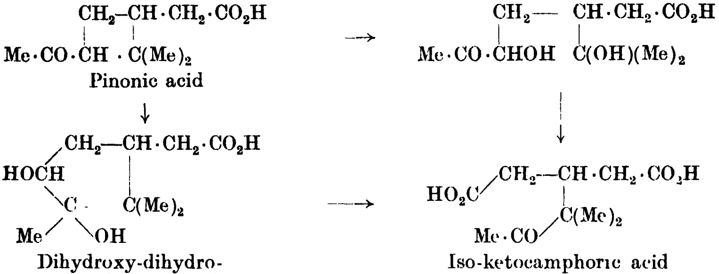
The course of the oxidation is shown in the following scheme:



The energetic action of bromine on pinonic acid in the presence of water leads to deep-seated changes with the formation of 2:4-dimethylphenylacetic acid (*Harispe*, C. r. **202**, 1591).

The degradation of pinonic acid and pinoylformic acid can be carried out in two other ways:

(1) By the action of chromic acid, pinonic acid gives **iso-ketocamphoric acid,** $C_{10}H_{16}O_5$, which is also obtained by the oxidation of campholenic acid (p. 301). The iso-ketocamphoric acid can be further degraded to **isocamphoronic acid,** $HO_2C\cdot CMe_2CH(CH_2CO_2H)_2$ (synthesis: *Perkin,* Proc. **16,** 214), and to **dimethyl-tricarballylic acid,** $HO_2C\cdot CMe_2CH(CO_2H)\cdot CH_2CO_2H$; the constitution of the latter acid is proved by splitting the corresponding hydroxy-acid (*Baeyer* and *Villiger,* Ber. **30,** 1959) into dimethylsuccinic acid and oxalic acid by fusion with potash (cf. hydroxycamphoronic acid, p. 315). The curious oxidation of pinonic acid to iso-ketocamphoric acid is not completely understood, but may be due to the formation of a dihydroxy compound which then undergoes the pinacol-pinacolin rearrangement (*Simonsen,* "The Terpenes", vol. II, p. 111). *Wagner* and *Slawinski* (Ber. **32,** 2080) have suggested that a rearrangement via dihydroxy-dihydro-α-campholenic acid may take place.

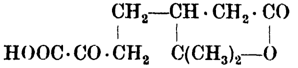


Pinonic acid

Dihydroxy-dihydro-α-campholenic acid

Iso-ketocamphoric acid

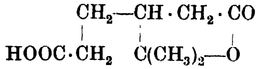
(2) When heated with acids (*Délépine,* C. r. **179,** 980), pinonic acid rearranges with hydrolytic fission into **homoterpenylic methyl ketone;** *semicarbazone* m.p. 200° (*Gandini,* Gazz. **64,** 594); this substance is a degradation product of α-terpineol (p. 223). In the same way, pinoylformic acid rearranges to **homoterpenoylformic acid,**



$$\begin{array}{lll} & \mathrm{CH_2{-}CH\cdot CH_2\cdot CO} & \\ \mathrm{HOOC\cdot CO\cdot CH_2} & \mathrm{C(CH_3)_2{-}O} & \end{array}$$

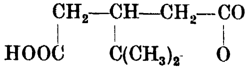
These rearrangement products give on further oxidation (*Baeyer,* Ber. **29,** 2775):

Homoterpenylic acid



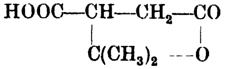
$$\begin{array}{ll} & \mathrm{CH_2{-}CH\cdot CH_2\cdot CO} \\ \mathrm{HOOC\cdot CH_2} & \mathrm{C(CH_3)_2{-}O} \end{array}$$

Terpenylic acid



$$\begin{array}{l} \mathrm{CH_2{-}CH{-}CH_2{-}CO} \\ \mathrm{HOOC \quad C(CH_3)_2 \quad O} \end{array}$$

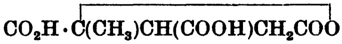
Terebic acid



$$\begin{array}{l} \mathrm{HOOC{-}CH{-}CH_2{-}CO} \\ \mathrm{\quad C(CH_3)_2{-}O} \end{array}$$

Terebic Acid, $C_7H_{10}O_4$, m.p. 175°, first obtained by oxidation of turpentine oil with nitric acid, is also formed by the oxidation of terpenylic acid, best with permanganate, and by the oxidation of isopropylsuccinic acid with chromic acid. Synthetically it can be obtained by the condensation of acetone with bromsuccinic ester by means of Zn—Cu, or by the action of MeMgI on acetylsuccinic ester (*Simonsen,* J. **91,** 184); cf. also teraconic acid (*Mahla* and *Tiemann,* Ber. **29,** 933; *Blaise,* C. r. **126,** 349; *Lawrence,* Proc. **15,** 104). It behaves similarly to paraconic acid (I, 612). When it is heated, **pyroterebic acid,** $(CH_3)_2C{:}CH\cdot CH_2CO_2H$ (I, 347), is formed with evolution of CO_2, together with **iso-caprolactone** and **teraconic acid,** $(CH_3)_2C{:}C(CO_2H)CH_2CO_2H$

(I, 573), which is reconverted into terebic acid by warming with mineral acids. With baryta, terebic acid gives the crystalline barium salt of diaterebic acid or hydroxyisopropyl-succinic acid. On oxidation with nitric acid terebic acid gives valerolactone-dicarboxylic acid (γ-methylbutyrolactone-β,γ-dicarboxylic acid) (*Bredt* and *Kershaw*, Ber. **32**, 3662)



$$CO_2H\cdot C(CH_3)CH(COOH)CH_2COO$$

For the formation of terebic acid from caronic acid see p. 31, and for methods of distinguishing it from caronic acid, which melts at the same temperature, see *Locquin*, Bull. **15** (1914), 747.

Terpenylic Acid, $C_8H_{12}O_4$, m.p. 90°, is formed by the oxidation of turpentine oil with chromic acid, and from homoterpenylic acid with nitric acid (*Baeyer*, Ber. **29**, 2789). It can be obtained synthetically by the action of CH_3MgI on β-acetylglutaric ester (*Simonsen*, J. **91**, 184). On distillation it gives **teracrylic acid,** $(CH_3)_2C:C(CH_3)CH_2CO_2H$ (I, 347). Terpenylic acid can be reduced to β-isopropylglutaric acid, which is oxidised back to terpenylic acid by chromic acid (cf. *Mahla* and *Tiemann*, Ber. **29**, 930, 2621; *Lawrence*, Proc. **15**, 104). For hydroxyterpenylic acid cf. p. 238.

Homoterpenylic acid, $C_9H_{14}O_4$, m.p. 102°, is formed by the oxidation of homoterpenylformic acid (see above) with fuming nitric acid or with lead oxide (*Baeyer*, Ber. **29**, 1916); it can be obtained synthetically from CH_3MgI and β-acetyladipic ester (*Simonsen*, J. **91**, 184).

Starting from pinene, homoterpenylic methyl ketone can thus be obtained in two different ways: (1) pinene is oxidised to pinonic acid and the 4-ring in this is opened hydrolytically; (2) pinene is transformed by hydrolysis into a monocyclic compound, terpin hydrate or α-terpineol, and this is oxidised.

Pinene hydrochloride, hydrobromide and **hydriodide**: see p. 252 and under **bornyl chloride, bromide** and **iodide** (p. 274).

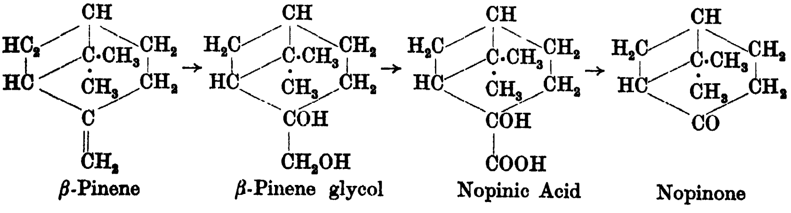
Pinene dichloride and **dibromide**: see p. 251 and under **dichlor-** and **dibrom-camphane** (p. 274).

Pinene nitrosochloride, $(C_{10}H_{16}NOCl)_2$, is obtained from α-pinene and NOCl, or amyl nitrite, acetic acid and hydrochloric acid (cf. e.g. *Rupe* and *Loffl*, Helv. **4**, 149); the decomposition point of the *dl*-form has been given as 115°, but depends the method of preparation and the rate of heating (*Ruzicka* and *Trebler*, Helv. **3**, 756). The *dl*-form of the nitrosochloride serves as a test for *dl*-α-pinene in essential oils, as it is much less soluble than the active form (*Lynn*, Am. **41**, 361). The latter, decomp. p. 89·5°, $[\alpha]^{20}_{D}$ + 396·2° (in benzene) (*Thurber* and *Thielke*, Am. **53**, 1030), is therefore unsuitable as a test for strongly active α-pinene. For this purpose pinonic acid is more frequently used. **dl-Pinene nitrosobromide,** decomp. p. 92°. Pinene nitrosochloride (p. 239) rearranges to hydrochlorocarvoxime when treated with HCl in ether (*Baeyer*, Ber. **29**, 12); with KCN it gives a *nitrosocyanide*, m.p. 171° (*Tilden* and *Burrows*, Proc. **18**, 161). By the action of aromatic bases such as aniline and toluidine upon the nitrosochloride, α-pinene is either regenerated or nitrolamine bases are formed, according to the conditions: **pinene nitrolaniline,** $C_{16}H_{22}ON_2$, m.p. (*dl*) 122°, (*Lynn*, Am. **41**, 361; *Earl* and *Kenner*, J. **1927**, 1269). On the other hand, ammonia and primary aliphatic bases (including benzylamine and piperidine) produce only nitrolamines, which are usually well crystalline: **pinene nitrolamine,** m.p. (*dl*) 137° (*Leach*, J. **91**, 1); **pinene nitrolbenzylamine,** m.p. (*dl*) 123–124°, (active) 144–145° (*Délépine*, *Alquier* and *Lange*, Bull. **1** (1934), 1250); **pinene nitrolpiperidine,** m.p. (*dl*) 119°, (active) 84°. Withs econdary aliphatic bases, such as diethylamine, or with sodium ethoxide, and even by heating in chloroform solution, pinene nitrosochloride splits up into HCl and **nitrosopinene,** a derivative of β-pinene (see below).

β-Pinene, *nopinene* (formula p. 256), b.p. 165·2°/760 mm., d^{20} 0·8708, n^{20}_{D} 1·4812, is found with α-pinene in American turpentine oils and to a greater extent in the French oils, usually as the laevorotatory form and almost optically pure: $[\alpha]_D$ between — 19·24° and — 22·5° (*Stephan*,

J. pr. **143**, 123). Abnormal rotatory dispersion: *Padmanabhan* and *Jatkar*, C. 1936 I 3515. β-Pinene has been shown to be present in a whole series of essential oils: the *l*-form in oil of hyssop (*Rutovski* and *Vinogradova*, J. pr. **120**, 46), in the oil from *Laurus nobilis* L. (*Morani*, C. 1926 I 2980), in pine-root and pine-needle oil (*Semmler* and *von Schiller*, Ber. **60**, 1591), etc.; the *d*-form in the oil of the ripe fruits of *Ferula galbaniflua* (*Rutovski* and *Vinogradova*, J. pr. **120**, 41), and as the chief constituent of the oil from the root of *Cynomarathrum Nuttallii* (*Nelson*, Am. **55**, 3400). It is isolated from these oils by careful fractional distillation, and separated from α-pinene (cf. *Austerweil*, C. 1926 I 2050). It can be obtained synthetically from nopinol-acetic acid (p. 262) by heating with acetic anhydride (*Wallach*, Ann. **368**, 9). It unites with hydrogen chloride to give a mixture of bornyl chloride, fenchyl chloride and dipentene dihydrochloride, because the primary addition product of HCl at the semicyclic double bond of β-pinene, i.e. true pinene hydrochloride (p. 251), undergoes further rearrangement. In the same way the addition of organic acids to β-pinene gives the same products as from α-pinene: β-pinene and picric acid give bornyl picrate, a little isobornyl and fenchyl picrates, and α-pinene, camphene, limonene and dipentene (*Délépine* and *Adida*, Bull. **39** [1926] 782; *Austerweil*, French Pat. 585,676 [1924] and 621,954 [1926]). Weak organic acids, e.g. benzoic, react under mild conditions with β-pinene to give α-pinene, together with quite small amounts of bornyl benzoate and dipentene (*Austerweil*, Bull. **39** (1926), 1643; *Austerweil* and *Petrovici*, ibid., 1732); α-pinene is also obtained from β-pinene by the action of palladium and hydrogen (*Richter* and *Wolff*, Ber. **59**, 1733). For the isomerisation of α- to β-pinene under the influence of SeO_2 see *Dupont* and *Zacharevicz*, C. r. **200**, 759. If β-pinene is hydrated with 45% sulphuric acid, terpin hydrate, also formed from α-pinene (p. 252), is obtained, together with a small quantity of the acid sulphate of pinene hydrate (see p. 259) (*Austerweil*, Bull. **39** (1926), 690). For the isomerisation of β-pinene to allo-ocimene see *Arbusov*, C. 1936 I 4736. β-Pinene differs from α-pinene in its behaviour towards nitrosyl chloride, mercuric acetate (*Gasopoulos*, Ber. **59**, 2184), N_2O_3 and $KMnO_4$. With N_2O_3 it combines to give a very unstable body containing the group $:C(NO)\cdot CH_2NO_2$, which is converted by ammonia or steam (*Wallach*, Ann. **346**, 243) into "**nitroterebenthene**" (*nitropinene*) $C_{10}H_{15}O_2N$. This substance is a mixture of nitro-compounds, in which the nitro-group is on the ω-carbon atom, and the double bond is partly in the α-pinene, partly in the β-pinene position. Reduction with zinc dust in acetic acid or with aluminium amalgam gives **ω-aminopinene**, $C_{10}H_{15}NH_2$, b.p. 80–81°/10 mm., d_4^{19} 0·932, n_D^{19} 1·4956, which by hydrogenation with Pt and H_2 gives the saturated **ω-aminopinane**, $C_{10}H_{17}NH_2$, b.p. 84–87°/11 mm., $d_4^{18.5}$ 0·9327, $n_D^{18.5}$ 1·49126 (*Ishikawa*, C. 1928 I 1062). ω-Aminopinene and nitrous acid give an alcohol which on oxidation with chromic acid gives tetrahydro-cuminaldehyde and the corresponding acid (*Wallach*, Ann. **346**, 246; cf. the analogous behaviour of β-phellandrene, p. 213).

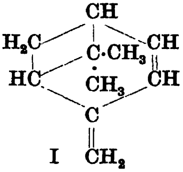
Oxidation of β-pinene with permanganate gives initially **β-pinene glycol**, $C_{10}H_{16}(OH)_2$, m.p. 76°, which goes further to **nopinic acid**, $C_{10}H_{16}O_3$, m.p. 126°, an α-hydroxy-acid characterised by its difficultly soluble sodium salt; this serves as a test for β-pinene. Oxidation with loss of CO_2 leads to the ketone **nopinone**, $C_9H_{14}O$ (p. 262) (*Wallach* and *Blumann*, Ann. **356**, 227; *Wallach*, ib. **368**, 9; *Nelson*, Am. **55**, 3400):

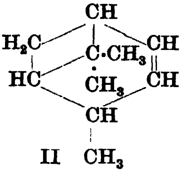

β-Pinene β-Pinene glycol Nopinic Acid Nopinone

Autoxidation of β-pinene leads to pinocarveol (p. 258) and pinocarvone (p. 261).

Further derivatives of β-pinene are **nitrosopinene,** $C_9H_{12}(:CH_2)(:NOH)$, m.p. 134°, which is obtained from pinene nitrosochloride (p. 255) by loss of HCl, and **pinylamine** $C_9H_{13}(:CH_2)(NH_2)$, b.p. 90°/12 mm., which is formed with pinocamphone (p. 262) by the reduction of nitrosopinene with zinc dust and acetic acid. By degradation with ozone both compounds lose one carbon atom to give ketones, derivatives of nopinone, which are **nitrosonopinone** and **α-aminonopinone** (as acetyl compound) (*Ruzicka* and *Trebler,* Helv. **4**, 566).

Verbenene, $C_{10}H_{14}$ (I), b.p. 158–159°/749 mm.,


I

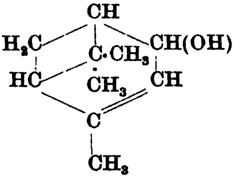

II

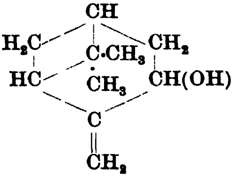
d^{15} 0·885 (*Blumann* and *Schmidt,* Ann. **453**, 48), is formed by the dehydration of verbenol, when the endocyclic double bond rearranges to the semicyclic position. Oxidation with permanganate gives cis-norpinic acid (*Blumann* and *Zeitschel,* Ber. **54**, 887; see p. 253). Reduction with sodium and alcohol gives α-pinene (cf. *Ruzicka* and *Pontalti,* Helv. **7**, 489); treatment with P_2O_5 or $ZnCl_2$ gives cymene. *Verbenene dibromide,* m.p. (active) 71–72°, (*dl*) 50–52°.

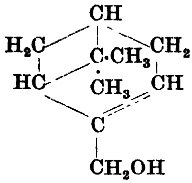
δ-Pinene, $C_{10}H_{16}$ (II), b.p. 157–158°/740·5 mm., d_4^{20} 0·8708, is formed by the thermal decomposition of verbanol methyl xanthate (*Wienhaus* and *Schumm,* Ann. **439**, 20) and of verbanyltrimethylammonium hydroxide. The reaction can go in one direction only, if the pinane system remains intact. Oxidation of the hydrocarbon leads to pinocamphoric acid (see under pinocamphone, p. 262). **Homopinene,** $C_{11}H_{18}$, see *Wienhaus* and *Schumm,* Ann. **439**, 29 and *Hasselstrom,* C. 1931 II 1411.

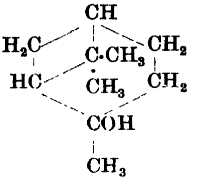
Pinane, $C_{10}H_{18}$, b.p. 166–168·5°, d_4^{20} 0·855–0·860, n_D^{20} 1·461–1·462, $[\alpha]_D$ + 16° — + 22°, is obtained from pinene by catalytic reduction with nickel and hydrogen at 220–230° or with platinum and hydrogen at ordinary temperatures (*Lipp,* Ber. **56**, 2099). As saturation of the double bond can give two stereoisomeric compounds, the hydrocarbons obtained by different methods vary somewhat in their physical properties. Pinocamphane, prepared from pinocamphone hydrazone and sodium ethoxide, also has the same formula (*Nametkin,* C. 1923 III 1156). For pinane from verbanone hydrazone see *Wienhaus* and *Schumm,* Ann. **439**, 36. The degradation of pinane with $KMnO_4$ gives *methylnopinol* $C_{10}H_{18}O$, m.p. 79°, stereoisomeric with *Wallach*'s methylnopinol (see below), pinonic acid $C_{10}H_{16}O_3$, and terebic acid $C_7H_{10}O_4$, typical oxidation products of α-pinene (pp. 253, 254). For the oxidative degradation to a cyclobutane derivative $C_{10}H_{18}O$ (*semicarbazone* m.p. 196°) see *Shochet,* Bull. Belg. **44**, 387. For the lower homologue, **nopinane,** C_9H_{16} cf. *Semmler* and *Feldstein,* Ber. **47**, 384.

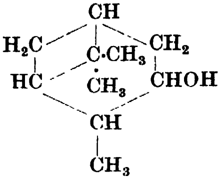
2. Alcohols.—A. Monohydric Alcohols:


(I)


(II)


(III)


(IV)


(V)

Verbenol, $C_{10}H_{16}O$ (I), b.p. 95°/9 mm., m.p. 8°, d^{15} 0·9745, n_D^{20} 1·4938, is present in the autoxidation products of α-pinene, but cannot be separated in the pure form from these (*Wienhaus* and *Schumm*, Ann. **439**, 20). It can be obtained pure, however, from the corresponding ketone, verbenone (p. 260), by reduction with isopropyl alcohol and aluminium isopropoxide (*Blumann* and *Schmidt*, Ann. **453**, 48). CrO_3 reconverts it to verbenone, while $KMnO_4$ degrades it to pinononic acid (p. 261). When it is converted to the acetate, verbenene (see above) occurs as the main product. By hydrolysis of the acetate a verbenol is obtained which can be re-oxidised to the original verbenone, but which has different physical properties from the above. Under the influence of the acetylating agent a mixture of the two possible stereoisomers is apparently formed.

Verbanol, *dihydro-verbenol,* $C_{10}H_{18}O$, m.p. 58°, b.p. 218°, is formed from verbenone by reduction with sodium in moist ether. Its acetate smells like bornyl acetate. *Acid phthalate* m p. 127°. Decomposition of its methyl xanthate gives δ-pinene (see above) (*Wienhaus* and *Schumm*, Ann. **439**, 20). With verbanol, as with menthol, four racemates (2 cis-, 2 trans-) and eight optically active forms (2 *d*-cis-, 2 *l*-cis-, 2 *d*-trans-, 2 *l*-trans-) are possible. For attempts to prepare stereochemically pure verbanols see *Vavon* and *Kahnemann*, Bull. **53**, (1933) 1167 (also see pinocampheol).

Pinocarveol, $C_{10}H_{16}O$ (II), m.p. (active) 7°, (*dl*) a liquid, b.p. 208–209°/750mm., 101·5–102°/20 mm., is contained as the *l*-form in the oil from *Eucalyptus globulus* (*Wallach*, Ann. **346**, 227), and is produced as the *d*-form in the autoxidation of *l*,β-pinene. *dl*-Pinocarveol is formed by the action of nitrous acid on pinylamine (p. 260) (*Wallach*, Ann. **346**, 221). *Phenylurethane* m.p. (active) 88–90°, (*dl*) 95–96°. Dilute sulphuric acid converts pinocarveol into a bimolecular *hydrate* $(C_{10}H_{18}O_2)_2$, m.p. (active) 190–191°, (*dl*) 176–177°. When boiled with sodium, pinocarveol rearranges into pinocamphone (p. 262) (*Schmidt*, Ber. **63**, 1129). Oxidation with CrO_3 gives pinocarvone (p. 261), and heating with potassium bisulphate or dilute sulphuric acid gives p-cymene. With ozone the semi-aldehyde of pinic acid is obtained (*semicarbazone* m.p. 174–176°), which can be oxidised further to pinic acid.

Myrtenol, $C_{10}H_{16}O$ (III), b.p. 223°, d^{20} 0·9763, $[\alpha]_D$ + 45° 45′, in the form of its acetate is the characteristic constituent of myrtle oil (*Penfold*, *Ramage* and *Simonsen*, Proc. Roy. Soc. N. S. W. **68** (1934) 36); *acid phthalate* m.p. 114–115°. *Myrtenyl chloride*, $C_{10}H_{15}Cl$, obtained by the action of PCl_5, gives *d*, α-pinene on reduction with Na and alcohol. Oxidation with chromic acid gives the corresponding aldehyde, *myrtenal* $C_{10}H_{14}O$ (p. 260), whilst catalytic hydrogenation with Pt gives **dihydromyrtenol,** *myrtanol* $C_{10}H_{18}O$, b.p. 108–110°/10 mm., $d_4^{9.7}$ 0·9801, $n_D^{9.7}$ 1·4918 (*d*-form); *p-nitrobenzoate* m.p. 90·5–91·5° (*P. Lipp*, private communication). For two isomeric forms, see *Dupont* and *Zacharewicz*, C. r. **199**, 365. Myrtenol can be degraded to d-pinic acid with permanganate (*Semmler* and *Bartelt*, Ber. **40**, 1363). Myrtenyl derivatives: cf.. *Rupe* and *Héritier*, Ann. **459**, 171. Myrtenol from α-pinene: *Zacharevicz*, Bull. Pin **3** (1935), 143.

Methylnopinol, *pinene hydrate* $C_{10}H_{18}O$ (IV, above), m.p. 59°, b.p. 205°, smells like camphor and is formed from nopinone and MeMgI, and as its acid sulphuric ester from β-pinene (*Austerweil*, Bull. **39** (1926), 690). Dilute sulphuric acid converts it into optically active α-terpineol (*Wallach*, Ann.

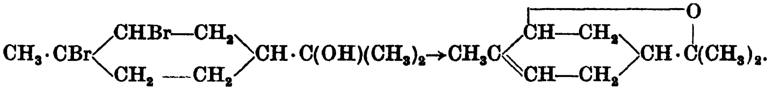
360, 88) and terpin hydrate, and with hydrogen halides in acetic acid it gives the dipentene di-hydrohalides. PCl_5 gives a very unstable *chloride*, b.p. 97—105°/13 mm., which may be identical or stereoisomeric with "true pinene hydrochloride" (*Wallach*, Ann. **356**, 239). For the isomeric methylnopinol from pinane and $KMnO_4$ see p. 257 and *Lipp*, Ber. **56**, 2099. For ethyl- and propyl-nopinol see *Wallach*, Ann. **360**, 91.

Pinocampheol, $C_{10}H_{18}O$ (V, p. 258), occurs as its *l*-form in oil of hyssop from the Crimea, and is obtained by reduction of pinocamphone (p. 262), into which it can be reconverted by oxidation (*Rutovski* and *Vinogradova*, C. 1927 II 1761), and by the catalytic reduction of pinocarveol. Like verbanol it can occur in four racemic and eight optically active forms. Two *l*- and two *d*-forms, and their respective racemates, are known. The cis-form is obtained by the catalytic reduction of pinocarveol; b.p. 219°/760 mm., m.p. (active) 57°, (*dl*) 42°, d^{15}_{15} 0·973, $[\alpha]_D$ approx. ± 36° (20% alcoholic solution), *phenylurethane* liquid, *acid phthalate* m.p. (active) 126°; and the trans-form by reduction of pinocamphone with sodium and alcohol, b.p. 217°/760 mm., m.p. (active) 67°, (*dl*) 36°; d^{15}_{15} 0·968, $[\alpha]_D \pm 55°$ (20% alcoholic solution), *phenylurethane* m.p. (active) 77°, (*dl*) 99°, *acid phthalate* m.p. (active) 107°, (*dl*) 113° (*Schmidt* and *Schulz*, Sch. & Co. Report **1934**, 91). The methyl xanthate of *l*-trans-pino- campheol, m.p 61°, gives on heating a mixture of α- and δ-pinene (*Ruzicka* and *Pontalti*, Helv. **7**, 489).

B. Polyhydric Alcohols.—α and β-Pinene glycols: see under the oxidation products of α- and β-pinene. The other alcohols described here do not contain the carbon skeleton of pinene, but are derivatives of p-menthane; they are included here on account of their close genetic relationships to pinene.

Pinol hydrate, *sobrerol*, *Δ^1-p-menthene-6:8-diol*, $C_{10}H_{16}(OH)_2$, is known in three forms. *d*- and *l*-Pinol hydrates, m.p. 150°, $[\alpha]_D$ ± 150°, can be obtained from *d*- and *l*-α-pinenes by atmospheric oxidation in sunlight, and by oxidation with mercuric acetate. Since α-pinene is usually not optically pure, **dl-pinol hydrate,** m.p. 131° (p. 252) is also obtained, and can easily be isolated because of its low solubility. This compound is also obtained by treating pinol with hydrobromic acid and alkali, and by mixing equimolecular quantities of *d*- and *l*-pinol hydrate. Pinol hydrate is formed from α-pinene by rupture of the bridge with the addition of two OH-groups. It still contains the double bond of α-pinene and therefore gives a *dibromide*, m.p. (*dl*) 131°, and with permanganate gives a tetrahydric alcohol, *p-menthane-1:2:6:8-tetrol*, the so-called **sobrerythritol,** $C_{10}H_{16}(OH)_4$, m.p. 156° (*Ginzberg*, Ber. **29**, 1195; *Wallach*, Ann. **291**, 351). An *isomeric* sobrerythritol, m.p. 194°, is obtained from the product of the action of HOCl upon α-pinene (p. 252) (*Wagner* and *Slavinski*, Ber. **32**, 2069). The catalytic reduction of pinol hydrate leads to menthane-2:8-diol (p. 221).

Pinol, *dl-sobrerone*, the anhydride of *Δ^1-p-menthene-6:8-diol* $C_{10}H_{16}O$, b.p. 183°, d^{20} 0·953, n_D 1·46949, optically inactive, is formed from the three pinol hydrates by the action of dilute sulphuric acid, and from the dibromide of α-terpineol (p. 223) by loss of 2 HBr. For an optically active form see *Wagner* and *Slavinski*, Ber. **32**, 2070. Like cineole (p. 220), it is indifferent towards hydroxylamine, phenylhydrazine and acid chlorides. These facts, as well as its formation from α-terpineol dibromide, are explained by the following formula:



α-Terpineol dibromide Pinol

Pinol hydrate is the hydrate corresponding to this oxide; it is an hydroxy-terpineol formed from pinene by rupture of the four-membered ring.

Pinol dibromide, $C_{10}H_{16}Br_2O$, m.p. 94°, b.p. 143°/11 mm., is converted into pinol by sodium or alcoholic potash. With hydrogen bromide the oxygen bridge is broken giving **pinol tribromide,** *1:2:8-tribrom-*p*-menthanol-6,* $C_{10}H_{17}Br_3O$, m.p. 160°, which by loss of HBr in another direction gives an isomeric **isopinol dibromide,** m.p. 94°; this, like pinol tribromide, gives *dl*-carvone with potash, and on reduction changes its 6-ring to a 5-ring giving a mixture of 3-isopropenyl-1-acetylcyclopentane and 3-isopropylidene-1-acetylcyclopentane ("*pinolone*") $C_{10}H_{16}O$ (*Wallach*, Ann. **384**, 193). Formic acid reduces pinol dibromide to cymene (*Wallach*, Ann. **268**, 225). **Pinol isonitrosochloride,** $C_{10}H_{16}O \cdot NOCl$, m.p. 131° (*Wallach*, Ann. **306**, 280) gives nitrolamines with bases.

cis-Pinol glycol, $C_{10}H_{16}O(OH)_2$, m.p. (*dl*) 125°, is obtained from pinol dibromide with silver oxide or lead hydroxide, and also from the corresponding *diacetate*, m.p. 97° (*Wallach*, Ann. **268**, 223). It is also formed from **pinol oxide,** $C_{10}H_{16}O_2$, b.p. 207°, with dilute acids. This latter is obtained from the pinene dichlorhydrins and alkali, and is the di-anhydride of sobrerythritol (above). **trans-Pinol glycol** is formed by the oxidation of pinol with permanganate: *diacetate* m.p. 37–38° (*Wallach*, Ber. **28**, 2710; *Slavinski*, C. 1898 II 543). **Pinol chlorhydrins,** $C_{10}H_{16}OCl(OH)$, m.p. 131°, are obtained from the pinene dichlorhydrins, the *d*- from *l*-pinene, and the *l*- from *d*-pinene (*Wagner* and *Slavinski*, Ber. **32**, 2070).

3. Bases. — **Pinylamine** $C_{10}H_{15}NH_2$, b.p. 207°, d 0·943, is formed by reduction of nitrosopinene (p. 257) (*Wallach*, Ann. **268**, 197). By the action of nitrous acid it is converted into pinocarveol (p. 258). For **ω-aminopinene** and **ω-aminopinane** see p. 256.

Dihydropinylamine, *pinocamphylamine* $C_{10}H_{17}NH_2$, b.p. 199°, from nitrosopinene by reduction with sodium and amyl alcohol (*Tilden* and *Shepheard*, J. **89**, 1560). For pinocamphylamine from pinocamphone oxime and its conversion into a mixture of α- and δ-pinenes see *Ruzicka* and *Pontalti*, Helv. **7**, 489.

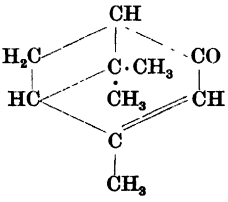
Verbanylamine, $C_{10}H_{17}NH_2$, b.p. 211°/750 mm., from verbanone oxime by reduction. *Oxalate* m.p. 131° (*Wienhaus* and *Schumm*, Ann. **439**, 38).

4. Aldehydes. — **Myrtenal** $C_{10}H_{14}O$, b.p. 92°/12·5 mm., d_D^{20} 0·9898, $[\alpha]_D$ + 15·68° (*Rupe*, Ann. **459**, 189), occurs in the *d*-form with perillyl aldehyde (p. 229) in "false camphor oil" (from *Hernandia peltata*), and is formed from myrtenol with chromic acid. Myrtenal has a fresh smell reminiscent of cinnamic aldehyde: *semicarbazone* m.p. 230°, *oxime* m.p. 71–72°. From the oxime, via the nitrile, *myrtenic acid* $C_{10}H_{14}O_2$, m.p. 54°, is obtained (*Semmler* and *Zaar*, Ber. **44**, 815; see also *Dupont*, *Zacharevicz* and *Dulou*, C. r. **198**, 1699).

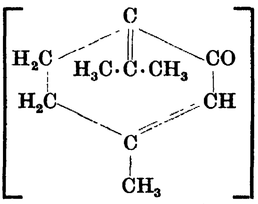
Dihydromyrtenal, $C_{10}H_{16}O$, from dihydromyrtenol and chromic acid; *semicarbazone* (active) m. p. 176°. The *oxime*, b.p. 93–95°/0·4 mm., gives aminopinane on reduction with Na and alcohol (p. 256); *hydrochloride* m.p. 271° (*P. Lipp*, private communication).

5. Ketones. — **Verbenone,** $C_{10}H_{14}O$ (formula p. 260) m.p. 6·5°, b.p. 233–234°/740 mm., d^{15} 0·9795, $[\alpha]_D$ + 249°, is obtained with verbenol by the autoxidation of oil of turpentine, by the catalytic oxidation of α-pinene with colloidal osmium (*Wienhaus* and *Schumm*, Ann. **439**, 20; *Suzuki*, C. 1935 II 526), and by oxidation of α-pinene with CrO_3 (*Treibs* and *Schmidt*, Ber. **61**, 459) or SeO_2 (*Schwenk* and *Borgwardt*, Ber. **65**, 1601; but cf. *Dupont*, *Zacharevicz* and *Dulou*, C. r. **198**, 1699); the *d*-form is obtained from Greek, and the *l*-form from French turpentine oils, i.e. the ketone has the same sign of rotation as the starting material. Verbenone, mixed with verbenol and other terpene alcohols (*Blumann* and *Schulz*, Ann. **478**, 303), occurs in frankincense or olibanum oil from *Boswellia Carterii*. It also occurs in Spanish verbena oil, from which its name is derived. *Semicarbazone* m.p. 208–209° (*dl*, 180–181°), *oxime* m.p. 119–120°. Boiling with 25% sulphuric acid decomposes verbenone into acetone and Δ^1-methyl-cyclohexene-3-one (cf. decomposition of pulegone, p. 235), which is oxidised to γ-acetylbutyric acid. The degradation of verbenone with permanganate and with ozone leads to **pinononic acid,** $C_9H_{14}O_3$, m.p. 131–132°, *semicarbazone* m.p. 204–206° (cf. *Fromm* and *Klein,* Ann. **425**, 208), which has been synthesized from norpinic acid (*Guha* and *Ganapathi,* Ber. **69**, 1185). Autoxidation of verbenone (*Treibs,* Ber. **66**, 1491), and the rearrangement of verbenone oxide leads to the semi-enolised diketone of the pinane series, **hydroxyverbenone,** $C_{10}H_{14}O_2$, m.p. 121°, *semicarbazone* m.p. 191° (cf. buchu camphor). With sodium in moist ether, verbenone gives verbanol, which is oxidised by chromic acid to

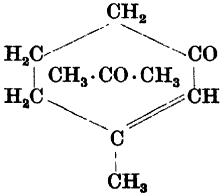
Verbanone, *dihydroverbenone* $C_{10}H_{16}O$. This compound is also obtained by the catalytic reduction of verbenone with Pd and hydrogen: b.p. 222°, d^{15} 0·9685, n_D^{20} 1·47535; *semicarbazone* m.p. 220–221°, *oxime* m.p. 88° (*Wienhaus* and *Schumm,* Ann. **439**, 35). The *hydrazone,* m.p. 27°, gives pinane when decomposed with sodium ethoxide, and verbanylamine (from the oxime by reduction) is converted into δ-pinene by exhaustive methylation and decomposition of the quaternary ammonium base. Strong mineral acids convert verbanone into o-menthenone, a reaction in which, apparently under the influence of the carbonyl group, the bridge is broken at a position usually untouched in rearrangements of the pinane system. *Isonitrosoverbanone,* $C_{10}H_{14}O(NOH)$, m.p. 139–140°, from verbanone with sodium and amyl nitrite, rearranges very easily into the isomeric pinocamphoric acid imide (see below), m.p. 96° (cf. the analogous change of isonitrosocamphor into camphoric acid imide); this like the isonitroso-body is hydrolysed to the mono-amide $C_{10}H_{17}O_3N$, m.p. 120°, of pinocamphoric acid.



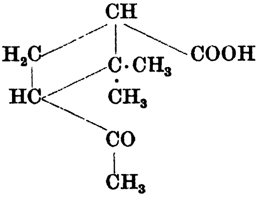
Verbenone



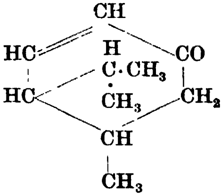
hypothetical



Δ^1-1-Methylcyclohexene-3-one and acetone



Pinononic Acid

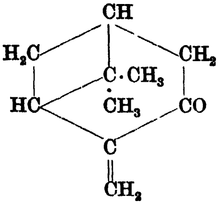


o-Menthenone from verbanone

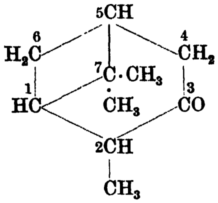
Carvopinone, $C_{10}H_{14}O$, b.p. 95°/12 mm. (*Wallach* and *Engelbrecht,* Ann. **346**, 231), is formed by heating nitrosopinene with aqueous oxalic acid. With hydroxylamine nitrosopinene is re-formed. Acids isomerise it readily to carvone. Its constitution is still unknown (*Ruzicka* and *Trebler,* Helv. **4**, 566), as is its relation to the isomeric

Pinocarvone, $C_{10}H_{14}O$ (I), b.p. 222–223°, 95°/12 mm., the oxidation product of pinocarveol (above). Like pinocarveol it is a derivative of β-pinene and is formed with pinocarveol in the autoxidation of β-pinene (*Schmidt,* Ber. **68**, 1129; cf. also its formation from β-pinene with SeO_2: *Dupont, Allard* and *Dulou,* Bull. **53** (1933), 599). *Semicarbazone* m.p. (active) 212–215°, (*dl*) 204°; *oxime* m.p. (active) 68–69°, (*dl*) 98°. It is degraded by permanganate to pinic acid (*Wallach,* Ann. **346**, 222).

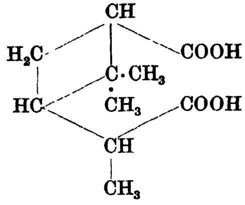
Pinocamphone, $C_{10}H_{16}O$ (II), b.p. 212–213°/752 mm.,



(I)



(II)



(III)

d_{15}^{15} 0·9692, occurs as its *l*-trans-form in oil of hyssop (from *Hyssopus officinalis* L.). *Semicarbazone* m.p. 227°; *dibromopinocamphone*, $C_{10}H_{14}OBr_2$, m.p. 93–95°. The *dl*-trans-form is obtained in the reduction of nitrosopinene with zinc and acetic acid together with pinylamine; *semicarbazone* m.p. 208°, *oxime* m.p. 89°; *dibromopinocamphone* m.p. 118–119°. *d*-cis-**Pinocamphone,** b.p. 212°/760 mm., d_{15}^{15} 0·966, from *l*-cis-pinocampheol by oxidation; *semicarbazone* m.p. 219°. The *oxime*, m.p. 88°, of the *dl*-cis-form is formed by the catalytic reduction of nitrosopinene (*Schmidt* and *Schulz*, Sch. & Co. Report **1934,** 91). The pinocamphones obtained from pinocarveol with aluminium isopropoxide (*Schmidt*, Ber. **62,** 103) or sodium (*id.*, *ib.* **63,** 1130) are not stereochemically pure. *dl*-cis-Pinocamphone can be synthesised from pinonic acid via homopinocamphoric ester (*Ruzicka* and *Trebler*, Helv. **4,** 666), a series of reactions which indirectly involves a partial synthesis of α- and δ-pinene. On oxidation with permanganate pinocamphone gives pinonic acid and *pinocamphoric acid*, $C_{10}H_{16}O_4$ (III), m.p. (*dl*) 186°, (active) 192°, isomeric with camphoric acid, because the 6-ring is attacked between C_2 and C_3 as well as between C_3 and C_4.

Nopinone (formula p. 256), m.p. ca. 0°, b.p. 209°, d^{20} 0·981, $[\alpha]_D$ + 18·48°, is an oxidation product of β-pinene (p. 255). *Benzylidene compound* m.p. 107°; *semicarbazone* m.p. 188°. With HCl in alcohol the difficultly soluble *trichloride* $C_{18}H_{29}OCl_3$, m.p. 148°, is formed by opening of the bridge and condensation of two molecules. Reduction of nopinone gives *nopinol*, in two stereoisomeric forms: m.p. (α) 102°, (β) 5–6°. When heated with dilute sulphuric acid it undergoes isomeric change to Δ^2-4-isopropylcyclohexenone (p. 115) (*Wallach* and *Blumann*, Ann. **356,** 227; *Komppa* and *Hasselstrom*, Ann. Acad. Sci. Fenn. A. **30** (1930), No. 14, 3). *Nopinolacetic acid* $C_9H_{14}(OH)CH_2COOH$, m.p. 84°, formed by condensation with bromacetic ester and zinc (*Wallach*, Ann. **363,** 7), forms the starting material for the partial synthesis of α- and β-pinene (p. 256) and of fenchene (p. 271). **Methylnopinone,** see *Kötz* and *Lemien*, J. pr. **90,** 314. **Ketonopinone,** $C_9H_{12}O_2$, m.p. 104°, from pinononic acid: *Guha* and *Ganapathi*, Ber. **69,** 1185.

IV. CAMPHANE GROUP[1]

The camphane group contains those compounds which possess a cyclohexane ring bridged in the 1:4-position by a single carbon atom (p. 180); they are found in nature in many essential oils, camphor being their most important representative. Since the systematic degradation of camphor has shown that a cyclohexane ring with a p-methylene bridge is a structure which can exist, attempts have been made to obtain substances with the carbon skeleton of camphor by starting with p-substituted hexahydrobenzene derivatives, e.g. by distillation of the Ca salt of trans-hexahydroterephthalic acid (*Zelinsky*, Ber. **34**, 3801), but without much success. The first complete synthesis of camphor involved: (1) the synthesis of camphor from camphoric acid, via homocamphoric acid (*Bredt*; *Haller*); and (2) the synthesis of camphoric acid (*Komppa*). A second complete synthesis of camphor was through camphene, which has been synthesised from a cyclopentanone derivative (*Komppa*) via camphenic acid (*Lipp*). Yet another total synthesis has been carried out with the aid of the diene method (p. 86): acrolein and cyclopentadiene give norcamphane-2-aldehyde, which gives norcamphor; methylation of this gives camphenilone, from which camphor can be obtained via camphene (*Diels* and *Alder*, Ann. **486**, 202; see also p. 285).

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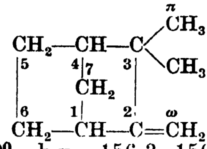
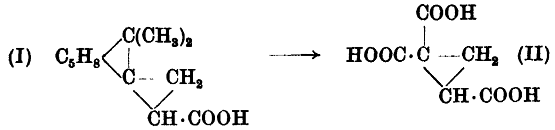
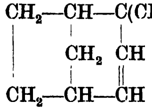
[1] The following monographs are useful: *Aschan*, Naphthenverbindungen, Terpene und Campherarten, Leipzig 1929; *Cornubert*, Le camphre et ses dérivés, Paris 1933.

1. Hydrocarbons. — Camphene,  *2-methylene-3:3-dimethyl-norcamphane*, m.p. 50°, b.p. 156·3—156·7°/712 mm., d^{51} 0·84224, n_D^{51} 1·45514 (*Brühl*, Ber. **25**, 162; *Lipp*, Ann. **382**, 282; *Aschan*, *ib.* **398**, 302), $[\alpha]_D^{20}$ + 99·5° (*W. Hückel* and *Nerdel*, *ib.* **528**, 73); cryoscopic constant approx. 270 (*Dulou*, Bull. Pin **2** (1934), 210), is the only naturally occurring terpene hydrocarbon which is solid at ordinary temperatures, it is known in a *d*-, an *l*- and an optically inactive (*dl*) form, all of which have the same chemical properties. Camphene is contained in many essential oils (*Stephan*, J. pr. **143**, 123), but always in small quantities, and its presence can be shown by converting it into isoborneol. It can be very easily prepared artificially from turpentine oils. The pinene hydrochloride obtained from these gives camphene on heating with sodium acetate and acetic acid at 200°, or by heating with aniline, pyridine, alkali phenates, sodium stearate, alkaline earth oxides and hydroxides and many other substances which eliminate HCl. Many such methods are protected by patents (cf. *Schering-Kahlbaum*, French Pat. 716,515 (1931); Brit.Pat.370,235 (1931); Germ.Pat.573,797 (1925); see p. 278), because camphene is an important intermediate in the technical preparation of camphor (p. 286). Camphene from strongly active pinene hydrochloride is either active or racemic, according to method of HCl-removal (*Lipp* and *Stutzinger*, Ber. **65**, 241). With the aid of suitable catalysts, camphene can also be obtained from α-pinene by direct rearrangement (p. 252). Isoborneol, on treatment with zinc chloride in benzene solution or by boiling with dilute sulphuric acid, is changed into camphene, whilst borneol is dehydrated by potassium bisulphate to give camphene only at 200°. Camphene hydrate (p. 279) and the stereoisomeric methylcamphenilol lose water very readily to give camphene.

Camphene contains one double bond, the semicyclic position of which causes an elevation in the molecular refraction (*Auwers*, Ann. **387**, 240; *Lipp*, *Götzen* and *Reinartz*, Ann. **458**, 1). The constitution of camphene is shown clearly, if not decisively, by the following facts: (1) the addition of diazoacetic ester to camphene (*Buchner* and *Weigand*, Ber. **46**, 759), and the degradation of the so-formed 3:3-dimethylnorcamphane-2-spirocyclopropane-carboxylic acid (I) to cyclopropane-1:1:2-tricarboxylic acid (II) (p. 33):

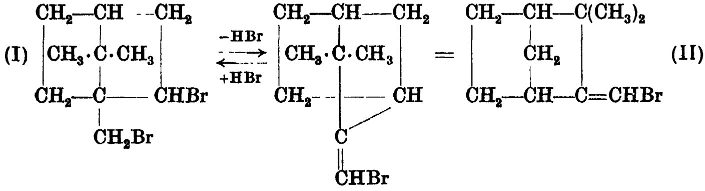


and (2) the oxidation with ozone (p. 268), which at least in part gives the normal fission products, camphenilone and formaldehyde. The fact that there is no endocyclic double bond is shown conclusively by the direct comparison of camphene with **endocamphene**, b.p. 170·6–171·6°/744·5 mm., $d_4^{12\cdot4}$ 0·8957, $n_D^{12\cdot4}$ 1·48442 (*Lipp*, *Götzen* and *Reinhardt*, loc. cit.):



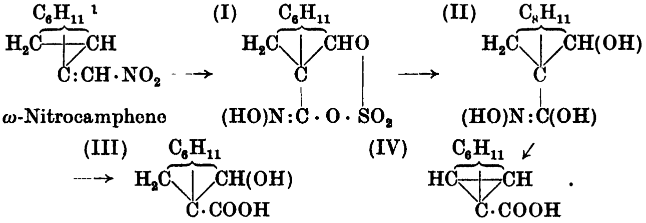
This has quite different chemical and physical properties.

From camphene and bromine in acetic acid solution **ω, 2-dibromcamphane,** $C_{10}H_{16}Br_2$ (I), m.p. 91°, is obtained, (*Lipp* and *Lausberg*, Ann. **436**, 279), together with liquid **ω-bromcamphene**, $C_{10}H_{15}Br$ (II), b.p. 226–228° (*Lipp*, J. pr. **105**, 57), which is also formed by heating ω, 2-dibromcamphane with dimethylaniline, HBr being eliminated, and which regenerates ω, 2-dibromcamphane with HBr (for the change from ω, 2-dibromcamphane to ω-bromcamphor, see p. 287):

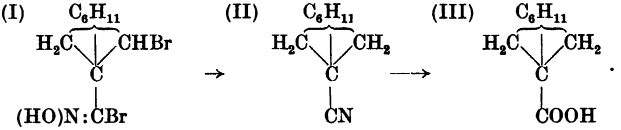


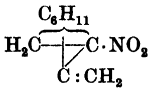
That ω, 2-dibromcamphane belongs to the camphane series is shown by the formation of ω-bromcamphoric acid when it is oxidised with nitric acid (*Lipp* and *Lausberg*, loc. cit.; cf. *Semmler*, Ber. **33**, 3427). ω-Bromcamphene gives with molten potash **dicamphenyl ether** b.p. 182°/9·5 mm.: $(C_9H_{14})\!:\!CHBr \rightarrow (C_9H_{14})\!:\!CHOK + BrCH\!:\!(C_9H_{14}) \rightarrow (C_9H_{14})\!:\!CH \cdot O \cdot CH\!:\!(C_9H_{14}) + KBr$. ω-Bromcamphene gives a Grignard compound, from which **dehydrodicamphene,** $(C_9H_{14})\!:\!CH \cdot CH\!:\!(C_9H_{14})$ and numerous ω-substituted derivatives of camphene can be obtained (*Langlois*, Ann. chim. (9) **12**, 364); see also ω-acetyl- and ω-benzoyl-camphene (*Lipp* and *Qvaedvlieg*, Ber. **62**, 2311).

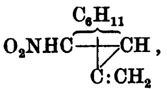
ω-Nitrocamphene, $C_8H_{14} > C\!:\!CHNO_2$ m.p. (*dl*) 66°, (active) 85°, b.p. 147°/12 mm., is amongst the products volatile with steam which are obtained by oxidising camphene with dilute nitric acid; it is also formed by the action of N_2O_3 on camphene, as a result of the loss of nitrous acid from the very unstable pseudonitrosite initially formed (*Lipp*, Ann. **399**, 241; **402**, 345). Treatment of ω-nitrocamphene with alcoholic potash gives **camphenilone** (p. 268) and potassium nitroacetate; alcoholic ammonia decomposes it into camphenilone and nitromethane. Reducing agents may give according to their nature and the conditions of reaction: **camphenilan-aldehyde** and ammonia, **camphenilan-aldoxime** or **ω-amino-isocamphane,** together with a little **di-isocamphylidene amine** (*Lipp*, *Dessauer* and *Wolf*, Ann. **525**, 279). If fuming nitric acid reacts in the cold with ω-nitrocamphene, rearrangement takes place with the formation of **ketopinic acid** (p. 297); cold concentrated sulphuric acid also causes a rearrangement, giving the cyclic sulphuric ester of **2-hydroxy-apocamphane-hydroxamic** acid (I), m.p. 127°, which can be hydrolysed easily to the free **acid** (II), m.p. 163–164°. The potassium salt of this acid is characteristic, and is used for its purification. With nitrous acid, the hydroxamic acid loses its nitrogen as nitrous oxide to give **2-hydroxy-apocamphane-carboxylic acid** (III), m.p. 240–242°, whilst in warm sulphuric acid solution **tricyclenic acid** (IV), m.p. 150–150·5°, is formed.



The action of hydrogen bromide on ω-nitrocamphene is analogous to that described for sulphuric acid; it gives **2-brom-apocamphane-hydroximic acid bromide** (I), m.p. 132–133°, which on reduction with zinc dust and acetic acid gives the **nitrile of apocamphane-carboxylic acid** (II), m.p. 171–172°; from this **apocamphane-carboxylic acid** (III), m.p. 221–222°, is obtained by hydrolysis:



1-Nitrocamphene, $C_{10}H_{15}O_2N$,  $\underset{C:CH_2}{\overset{C_6H_{11}}{H_2C\text{—}C\cdot NO_2}}$, (*Lipp* and *Lausberg*, loc. cit.), m.p. 56°, is obtained by HBr-elimination with $AgNO_3$ from **2-brom-2-nitrocamphane,** the reaction product of hypobromous acid and camphoroxime (*Lipp*, Ann. **399**, 244). The reduction of 1-nitrocamphene with zinc dust and acetic acid leads to **1-aminocamphene,** m.p. 46°, b.p. 191–192°, which with nitrous acid gives **1-hydroxycamphene,** m.p. 74°, b.p. 212°: *methyl ether* b.p. 193–194°. It should be noticed that 1-hydroxycamphene readily rearranges into camphor under the influence of acids.

6-Nitrocamphene, $C_{10}H_{15}O_2N$,  $\underset{C:CH_2}{\overset{C_6H_{11}}{O_2NHC\text{—}CH}}$, b.p. 119–119·5° (*Nametkin* and *Zabrodin*, Ann. **441**, 181), is formed by heating tricyclene with dilute nitric acid in a sealed tube at 125–130°; being a secondary nitro-compound it is soluble in alkali. *Pseudonitrol* $C_{10}H_{14}N_2O_3$, m.p. 99° (decomp). **6-Amino-camphene** is formed by the reduction of 6-nitrocamphene with stannous chloride, together with **camphenone,** *6-ketocamphene,* m.p. 78° (*Nametkin* and *Zabrodin*, Ber. **59**, 368). The quaternary ammonium base of 6-aminocamphene gives on distillation **isocamphodiene,** *camphenene-5,* (*Nametkin* and *Zabrodin*, Ber. **61**, 1491).

1-Chlorcamphene (I), m.p. ca. 20°, b.p. 193–197°, is formed by loss of HCl from 2:2-dichlorcamphane (p. 274), the product of the action of

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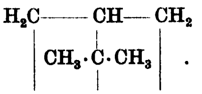
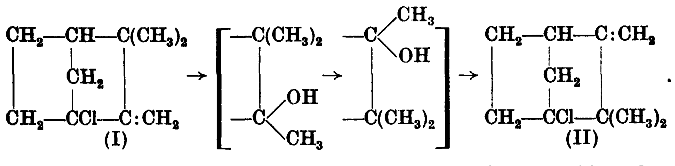
[1] The residue C_6H_{11} is  .

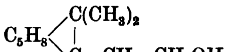
PCl_5 upon camphor (*Meerwein* and *Wortmann*, Ann. **435**, 190; *Houben* and *Pfankuch*, Ann. **489**, 204). It rearranges in the presence of catalysts, e.g. $SbCl_5$, to **4-chlorcamphene** (II), m.p. 123–129° (contains chlor-tricyclene) in which a methyl group is exchanged for an OH group in the intermediate compound without any change in the ring system:



With acetic and sulphuric acids 4-chlorcamphene forms 4-chlorisobornyl acetate (p. 300), a reaction analogous to the formation of isobornyl acetate from camphene (p. 279).

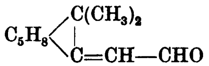
By heating camphene with trihydroxymethylene, **ω-methylol-camphene** (I) is obtained, which can be oxidised with CrO_3 to **camphenylidene-acetaldehyde** (II), b.p. 130°/12 mm. **ω-Methylcamphene** (III), b.p. 178°, is obtained from the latter by reduction with amalgamated Zn and HCl (Clemmensen's method). Energetic oxidation of ω-methylol-camphene with CrO_3 leads to **camphenylidene-acetic acid** (IV), m.p. 124–125°, b.p. 181°/19 mm. The carboxyl group stabilises the camphene nucleus, and prevents it from rearranging into the camphane system. Boiling with formic acid in fact gives the β-lactone (V) (*Langlois*, Ann. chim. (9) **12**, 193, 364; Bull. **41** (1927), 384):

(I)



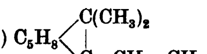
$\mathrm{C_5H_8}\left\langle\begin{array}{l}\mathrm{C(CH_3)_2}\\ |\\ \mathrm{C{=}CH{-}CH_2OH}\end{array}\right.$

(II)



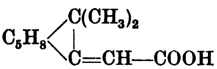
$\mathrm{C_5H_8}\left\langle\begin{array}{l}\mathrm{C(CH_3)_2}\\ |\\ \mathrm{C{=}CH{-}CHO}\end{array}\right.$

(III)



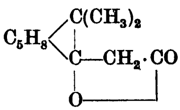
$\mathrm{C_5H_8}\left\langle\begin{array}{l}\mathrm{C(CH_3)_2}\\ |\\ \mathrm{C{=}CH{-}CH_3}\end{array}\right.$

(IV)



$\mathrm{C_5H_8}\left\langle\begin{array}{l}\mathrm{C(CH_3)_2}\\ |\\ \mathrm{C{=}CH{-}COOH}\end{array}\right.$

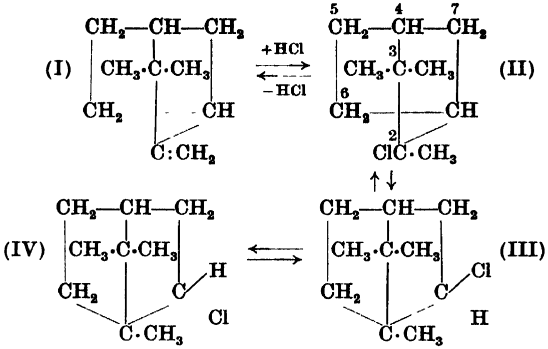
(V)



$\mathrm{C_5H_8}\left\langle\begin{array}{l}\mathrm{C(CH_3)_2}\\ |\\ \mathrm{C{-}CH_2{\cdot}CO}\\ |\qquad\quad\ \ |\\ \mathrm{O{-\!\!-\!\!-\!\!-}}\end{array}\right.$.

1-Methylcamphene, $C_{11}H_{18}$, m.p. 43°, is formed from tertiary methylfenchol (from magnesium methyl iodide and fenchone) by dehydration which takes place without rearrangement of the ring-system. In the Bertram-Walbaum reaction it undergoes rearrangement firstly into 4-methylcamphene (see below) by migration of a methyl group (cf. the change from 1- to 4-chlorcamphene, above; if CH_3 replaces Cl, the formulae show the rearrangement of 1- into 4-methylcamphene), and then into 4-methylisoborneol (Nametkin rearrangement) (p. 267; cf. *Lipp* and *Stutzinger*, Ber. **65**, 243). From this, as in the formation of camphene from isoborneol, **4-methylcamphene,** m.p. 120°, can be obtained (*Bredt-Savelsberg* and *Buchkremer*, Ber. **64**, 600). For **4-phenylcamphene,** $C_{16}H_{20}$, see *Nametkin, Kitchkin* and *Kurssanov*, J. pr. **124**, 144.

Camphene hydrochloride, $C_{10}H_{17}Cl$, m.p. 125–127° (*Meerwein* and *van Emster*, Ber. **53**, 1815), the chloride corresponding to camphene hydrate (*Aschan*, Ann. **410**, 223), is formed from camphene with gaseous HCl. Being a tertiary chloride, it is distinguished by the great mobility of its chlorine atom, and by the ease with which it loses HCl to give camphene again. When camphene hydrochloride is kept, the HCl evolved causes a gradual rearrangement into isobornyl chloride (p. 274). Between camphene hydrochloride (II) and isobornyl chloride (III) on the one hand, and between isobornyl chloride and bornyl chloride (IV) on the other hand, equilibria are set up (*Meerwein* and *van Emster*, Ber. **55**, 2500). The same relationship exists between the esters of camphene hydrate, isoborneol and borneol (*Meerwein*, Ann. **453**, 16) (formulae II, III and IV with OAc instead of Cl):



The rearrangement of camphene (I) via (II) into (III), which occurs by exchange of the Cl atom on C_2 to C_6, the five-membered ring (1, 2, 3, 4, 7) becoming the six-membered ring (1, 2, 6, 5, 4, 7), is closely related to the displacement of the atoms which takes place in the rearrangement of tetramethylethylene into pinocalin-alcohol or its chloride (retropinacolinic change). The formation of isobornyl and bornyl esters from camphene by the action of organic acids occurs in exactly the same way (*Semmler* and *Mayer*, Ber. 44, 2012). If sulphuric acid is added to the reaction mixture, the ester formation is accelerated and leads almost exclusively to isobornyl esters (*Bertram-Walbaum reaction*). The formulae given above (with OAc in place of Cl) do not however cover all phases of the formation of isoborneol from camphene. Consideration of the optical activity of the initial and rearranged products (*Lipp* and *Stutzinger*, loc. cit.), as well as the results with substituted camphenes (camphene-carboxylic acid, *Bredt*, J. pr. **131**, 141; 1-chlorcamphene, *Houben* and *Pfankuch*, Ann. **507**, 37; see also *Nametkin* and *Shawrygin*, C. 1936 I 559), lead to the assumption that in the rearrangement of camphene into isobornyl ester under the catalytic influence of mineral acids, one step in the series of reactions is the migration of a methyl group, as in the formation of santene from camphenilol (*Bredt-Savelsberg* and *Buchkremer*, Ber. **66**, 1925).

The *Wagner rearrangement* with ring-isomerisation (formulae I—III, above), combined with migration of a methyl group, as in the change from 1- to 4-chlorcamphene (p. 266), is known as the *Nametkin rearrangement*. For the addition of SO_3 to camphene, see *Lipp* and *Holl*, Ber. **62**, 499.

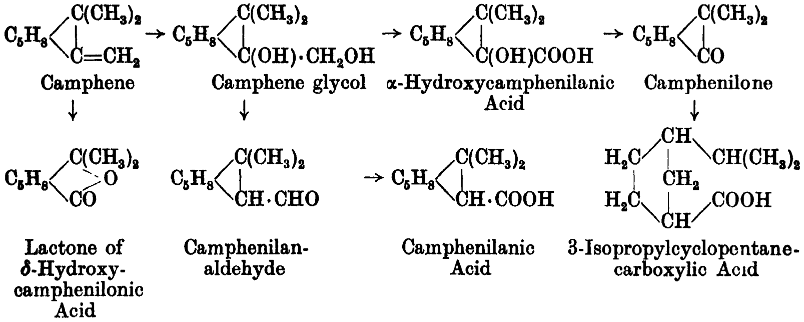
By the **oxidation** of camphene with CrO_3 and dilute sulphuric acid, camphor is formed, isoborneol sulphate being formed as an intermediate product which immediately decomposes. This process was at one time carried out commercially for the preparation of synthetic camphor.

The **reduction** of camphene may be carried out catalytically and gives **isocamphane** (p. 274), corresponding to camphene hydrochloride.

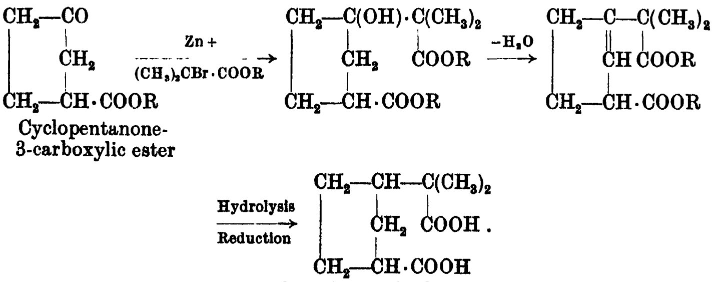
In the **oxidation** of camphene with $KMnO_4$ (*Moycho* and *Zienkovski*, Ann. **340**, 17) the initial product is **camphene glycol,** $C_{10}H_{16}(OH)_2$, m.p. 200°, which is dehydrated by dilute sulphuric acid to **camphenilanaldehyde,** $C_{10}H_{16}O$, m.p. 70°, b.p. 96°/14 mm. (*Semmler*, Ber. **42**, 962). This aldehyde can also be obtained from the chromyl chloride compound of camphene, $C_{10}H_{16}$-$(CrO_2Cl_2)_2$, by decomposition with water (*Bredt* and *Jagelki*, Ann. **310**, 119; cf. *Detoeuf*, Bull. **31** (1922), 169, 176). For its formation in the animal body after feeding with camphene, see *Fromm*, *Hildebrandt* and *Clemens*, C. 1903 I 594. On oxidation, camphenilanaldehyde gives two stereoisomeric acids $C_{10}H_{16}O_2$, **camphenilanic acid,** m.p. 65°, and **isocamphenilanic acid,** m.p. 118°. The latter has been obtained synthetically by hydrogenation of the adduct from cyclopentadiene and β,β-dimethylacrylic acid (*G. Komppa* and *O. Komppa*, Ber. **69**, 2608); Bi-salt, see C. 1936 I 812. The acids $C_{10}H_{16}O_2$

can be converted through the corresponding α-bromo-acids, into **hydroxycamphenilanic acid,** $C_{10}H_{16}O_3$, m.p. 171° (*Bredt* and *Jagelki*, Ann. **310**, 131). This acid is obtained directly from camphene glycol by oxidation with $KMnO_4$; on further oxidation it loses CO_2 and gives a ketone, **camphenilone,** $C_9H_{14}O$, m.p. (*d,l*) 39°, (act.) 37–38·5° (*P. Lipp*, Ann. **382**, 297; **399**, 250), b.p. 81°/12 mm., a lower homologue of fenchone (p. 315), to which it is very similar in odour and behaviour. Camphenilone is degraded by the action of sodamide to the amide of 3-isopropylcyclopentane-carboxylic acid (*Semmler*, Ber. **39**, 2580); this acid can be degraded further to 3-isopropylcyclopentanone (*Bouveault* and *Blanc*, C. r. **146**, 233), and has been synthesised from β-isopropyladipic acid (*Bouveault* and *Blanc*, ib. **147**, 1314).

The ozonide of camphene (*Lipp*, *Götzen* and *Reinartz*, Ann. **458**, 2) is decomposed by water or acetic acid to give camphenilone and a product of the fission of the camphene ring, the lactone of **δ-hydroxycamphenilonic acid** (*Harries* and *Palmén*, Ber. **43**, 1432), which can be obtained synthetically by the action of magnesium methyl iodide on the anhydride of cyclopentane-1:3-dicarboxylic acid (p. 63) (cf. the analogous fission of cyclic ketones with permonosulphuric acid, p. 108) (*Baeyer* and *Villiger*, Ber. **33**, 858). These various changes are easily understood with the aid of Wagner's camphene formula (p. 263):


Camphene
Camphene glycol
α-Hydroxycamphenilanic Acid
Camphenilone
Lactone of δ-Hydroxy-camphenilonic Acid
Camphenilan-aldehyde
Camphenilanic Acid
3-Isopropylcyclopentane-carboxylic Acid

Besides these compounds, the oxidation of camphene with $KMnO_4$, but not with ozone, gives large quantities (about 60% of the oxidation products) of a dicarboxylic acid isomeric with camphoric acid (p. 304), **camphenic acid** (camphene-camphoric acid), $C_{10}H_{16}O_4$, m.p. (*dl*) 136°, (active) 144° (*Aschan*, Ann. **375**, 336), the constitution of which has been proved by the following synthesis (*P. Lipp*, Ber. **47**, 873):

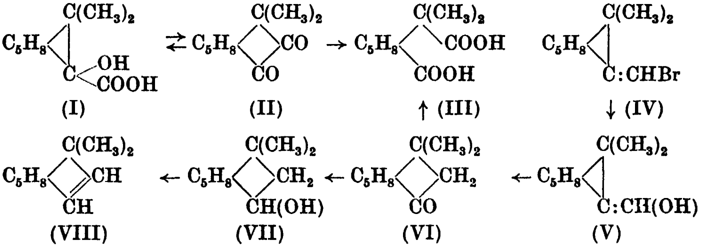


Camphenic Acid

This synthesis is interesting because it gave an indication how 1-methyl cyclopentane-1-carboxylic-3-acetic acid could be synthesized (see synthesis of fenchone, p. 316).

Synthesis of Camphene. — The synthesis of camphenic acid is of especial importance, because the lead salt of this acid on distillation gives camphenilone (*Komppa* and *Hintikka*, Ber. 47, 1551; cf. the synthesis of camphor from the Ca or Pb salt of homocamphoric acid), and this compound had been converted much earlier into tertiary methylcamphenilol (*Moycho* and *Zienkowski*, Ann. **340**, 61) and thus into camphene. The synthesis of camphenic acid, therefore, made the complete synthesis of camphenilone and camphene possible (cf. the diene synthesis of camphenilone, *Diels* and *Alder*, Ann. **486**, 202).

Camphenic acid is not formed directly from camphene, but through **α-hydroxycamphenilanic acid** (I). This gives firstly, by a retrobenzilic change, **carbocamphenilonone** (II), m. p. 59°, which is oxidised to camphenic acid (III). In a similar way, ω-bromcamphene (IV) (p. 264) on fusion with potash gives, via the hypothetical alcohol (V), the ring-**homocamphenilone** (VI), m.p. 39°, which is oxidised quantitatively to camphenic acid. In this reaction a ring-enlargement from a 5-ring to a 6-ring takes place, but this is different from that described in the camphene rearrangement. From the alcohol (VII), m.p. 13–16°, obtained by reduction of ring-homocamphenilone (VI), **endocamphene** (VIII) (p. 264) is formed by dehydration with zinc chloride. On the other hand, carbocamphenilonone (II), on warming with dilute caustic soda, is transformed back again into α-hydroxycamphenilanic acid (I), a reaction in which a ring-contraction similar to the benzilic acid rearrangement takes place (*Hintikka*, Ann. Acad. Sci. Fenn. A. 1919, **6**, No. 3):

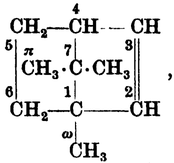


The dry distillation of camphenic acid gives **camphenilone-1-carboxylic acid,** m.p. (active) + $1H_2O$ 70°, anhyd. 105–106°, (*dl*) 134° (*Aschan*, Ann. **410**, 240), which, although a β-ketonic acid, is very stable, and shows as little tendency to lose CO_2 on heating as the isomeric **ketopinic acid,** m.p. 234° (*Bredt*, C. 1927 II 2298) (formulae, p. 298). Ketopinic acid is the oxidation product of 2-hydroxyapocamphane-carboxylic acid (p. 265).

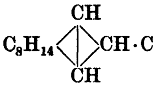
When camphene is oxidised with dilute nitric acid the tribasic **carboxy-apocamphoric acid,** $C_7H_{11}(COOH)_3$, m.p. 196° is formed. The course of this reaction is best explained by assuming that, as in the oxidation of camphene by $KMnO_4$ to camphenic acid, α-hydroxy-camphenilanic acid is the intermediate product, which undergoes a rearrangement in the acid medium, similar to that of camphene hydrate to isoborneol. The 2-hydroxyapocamphane-carboxylic acid (p. 265, formula III) thus formed is immediately oxidised to the tricarboxylic acid (p. 298).

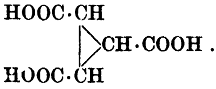
For the use of camphene in cryoscopic molecular weight determinations, see *Pirsch*, Ber. **65**, 862.

Under special conditions it is possible to avoid molecular (pinacolinic) rearrangements in the dehydration of borneol and the elimination of halogen halide from bornyl halides, and thus to obtain

Bornylene, 

, m.p. 113°, b.p. 146°, $[\alpha]_D$ — 23·94° (c = 8·23 in benzene). An isomeric bornylene with the double bond in the 3:4-position does not exist It has been shown in general that in the camphane and pinane systems and in similarly constituted compounds a carbon-carbon double bond is never formed at the junction of the carbon bridge (the "bridge-head") (*Bredt's Rule*; Ann. **437**, 1). Bornylene is notable for its great volatility (*Bredt*, Ann. **366**, 52; *Bredt* and *Perkin jun.*, J. pr. **89**, 257). It is formed from bornyl iodide with conc. alcoholic potash (*Kondakov*, C. 1910 I 2089); by heating bornyl chloride with potassium amyloxide in an autoclave at 230–240° a bornylene of m.p. 107–108° is obtained which contains 10% of camphene, from which it can be purified by treatment with benzoyl peroxide (*Meerwein*, J. pr. **113**, 9). By the dry distillation of bornyl methylxanthate (*Tchugaev* and *Budrick*, Ann. **388**, 280) bornylene is formed together with camphene and tricyclene (*Nametkin* and *Brüssov*, J. pr. **112**, 169). From epibornyl xanthate, however, bornylene m.p. 113° is obtained free from camphene (*Bredt* and *Perkin jun.*, J. pr. 89, 256). Pure bornylene was first obtained from bornylene-carboxylic acid (p. 296) by loss of CO_2 (*Bredt* and *Hilbing*, J. pr. 84, 782). A further method of preparation is the decomposition of bornyltrimethylammonium hydroxide (*Ruzicka*, Helv. **3**, 748). Bornylene condenses with diazoacetic ester to the tricyclic compound (I), the hydrolysis of which gives the acid $C_{12}H_{18}O_2$, m.p. 137°. Oxidation of this acid with $KMnO_4$ in sulphuric acid solution gives trans-cyclopropane-1:2:3-tricarboxylic acid (II) (*Buchner* and *Weigand*, Ber. **46**, 2108; p. 33):

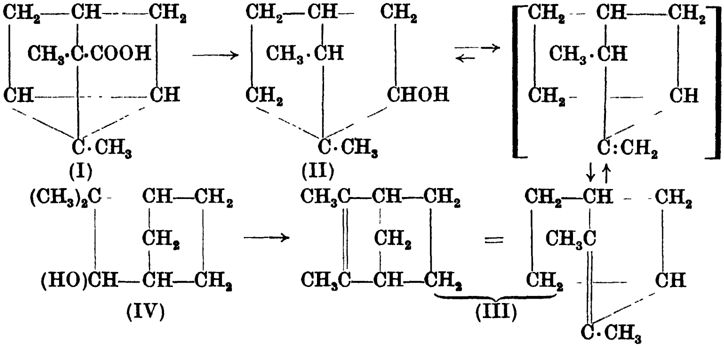
(I) 

(II) 

Bornylene is oxidised by $KMnO_4$ to camphoric acid (p. 304). *Nitrosite* m.p. 163°. With the calculated quantity of chlorine bornylene forms *2:3-dichlorcamphane* $C_{10}H_{16}Cl_2$, m.p. 126°, which is also obtained by the direct chlorination of bornyl chloride (*Gandini*, Gazz. **66**, 357).

The lower homologue of bornylene, **apobornylene,** C_9H_{14}, m.p. 38°, b.p. 136–137°/755 mm., in which the ω-methyl group is lacking, is formed with other hydrocarbons by the action of sodium on camphenilone dichloride, and by the decomposition of camphenilol xanthate (*Hintikka* and *Komppa*, Ann. **387**, 297; *Komppa* and *Roschier*, *ib.* **429**, 175; *Komppa* and *Hasselström*, *ib.* **497**, 116; *Lipp* and *Daniels*, Ber. **69**, 586, 2251). Its *ozonide* $C_9H_{14}O_3$, m.p. 55° (decomp.), decomposes to give apocamphoric acid. **Norbornylene,** C_7H_{10}, m.p. 52–54°, is formed from norborneol by dehydration (*Komppa* and *Beckmann*, Ann. **512**, 184).

Santene C_9H_{14} (III), b.p. 140°, d_4^{17} 0·8700, has been found in the first runnings from East Indian sandalwood oil, in Siberian pine-needle oil and in other needle-oils (*Aschan*, Ber. **40**, 4918), and is formed by boiling the tricyclic **teresantalic acid** (I) (p. 333), which also occurs in sandalwood oil in the form of its esters, with dilute sulphuric acid. In this reaction santene is formed via π-**apoisoborneol** (II), which undergoes a camphene rearrangement, the semicyclic double bond subsequently migrating into the ring; santene undergoes the reverse rearrangement into π-apoisiborneol when treated with acetic and sulphuric acids (*Semmler* and *Bartelt*, Ber. **41**, 125, 866; see also *Ruzicka* and *Liebl*, Helv. **6**, 267). Santene is also formed from camphenilyl chloride (IV, Cl instead of OH) by loss of HCl (*Jagelki*, Ber. **32**, 1503), and by the dehydration of camphenilol (IV), when a methyl group migrates ("santene rearrangement") (*Komppa* and *Hintikka*, Bull. **21**, (1917), 13; cf. *Semmler* and *Bartelt*, Ber. **41**, 125; *Komppa* and *Nyman*, Ber. **69**, 334):



Ozonisation of santene gives **1:3-diacetylcyclopentane** $C_5H_8(COCH_3)_2$, b.p. 119–124°/10 mm., *dioxime* m.p. 129° (*Semmler* and *Bartelt*, Ber. **41**, 128; cf. p. 194). Treatment of this ketone with alkaline hypobromite gives trans-cyclopentane-1:3-dicarboxylic acid (p. 36) (*id. ib.* 385). Santene gives an addition product with Hg-acetate, $C_{11}H_{18}O_3Hg$, m.p. 126–127° (*Deussen*, J. pr. **114**, 111). Santene is characterised by its beautiful blue *nitrosochloride* m.p. 109–110°. *Nitrosite* m.p. 124–125°, *hydrochloride* m.p. 80–81°, *santene-phenylazide* m.p. 86° (*Alder* and *Stein*, Ann. **485**, 213). The complete synthesis of santene has been carried out with the aid of the diene synthesis (p. 86): cyclopentadiene and crotonaldehyde give, after hydrogenation and oxidation of the primary adduct, 3-methyl-norcamphor; this is converted with MeMgI into γ-**santenol**, m.p. 63–65°, which is dehydrated by $KHSO_4$ to santene (*Diels* and *Alder*, Ann. **486**, 205).

Dicyclopentadiene $C_{10}H_{12}$, formed by the condensation of two cyclopentadiene molecules (p. 188), is a norbornylene substituted in the 5:6-position by an unsaturated 5-ring (*Alder* and *Stein*, Ann. **504**, 228). In the diene synthesis cyclopentadiene and its derivatives normally give compounds with the ring-system of norbornylene (pp. 22, 86, 181) (see also *Dilthey*, *Schommer* and *Trosken*, Ber. **66**, 1627).

The name "**fenchenes**" has been given to a series of hydrocarbons of the composition $C_{10}H_{16}$, which have not definitely been found in nature. They have the gem-dimethyl group sometimes in the bridge, sometimes in the six-ring, and have either a semicyclic or endocyclic double bond; their name comes from the fact that they are obtained from fenchyl and isofenchyl derivatives (*Komppa* and *Beckmann*, Ann. **509**, 51).

α-Fenchene (II) (D, *l*- and L, *d-fenchene*[1], *isopinene*, *β-pinolene*), b.p. 155–156°, d_4^{17} 0·8670, $[\alpha]_D$ — 32·12°, is formed by the action of nitrous acid on fenchylamine (*Wallach*, Ann. **362**, 192), and by the decomposition of methyl fenchyl xanthate, b.p. 162°/18 mm. In the latter method, cyclofenchene is also formed, but this gives the same HCl-addition product as α-fenchene, and this hydrochloride on boiling with o-toluidine gives α-fenchene (*Qvist*, Ann. **417**, 278; *Nametkin*, J. pr. **106**, 25). Some α-fenchene is obtained in the dehydration of fenchyl alcohol (I) with $KHSO_4$, in a way similar to the formation of camphene from isoborneol; β-fenchene (III) is the chief product, and other fenchenes are also formed:

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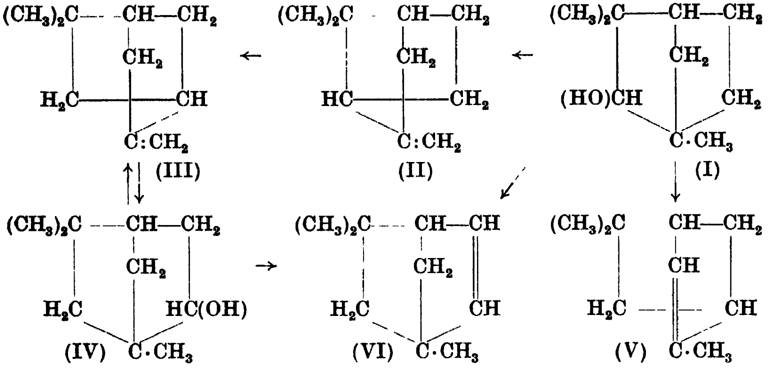
[1] The capitals D and L indicate, according to Wallach's suggestion, the directions of rotation of the *d*- and *l*-fenchones used for the preparation (see also *Komppa* and *Roschier*, C. 1917 I 407).



(IVa): Cl instead of (OH); (IVb): O·$COCH_3$ instead of (OH)

α-*Fenchene hydrochloride*, m.p. (*dl*) 35–37°, b.p. 81°/12 mm.; α-*fenchene dibromide*, m.p. (active) 88°, (*dl*) 62° (*Wallach*, Ann. **362**, 182). The oxidation of α-fenchene with $KMnO_4$ gives *hydroxy-α-fenchenic acid*, m.p. 155° (*Qvist*, Ann. **417**, 303), and then cis-*apocamphoric acid*, m.p. 206°. The degradation of α-fenchene with ozone leads to α-*fenchenylanic acid* (*apocamphane-2-carboxylic acid*), m.p. (active) 72°, (*dl*) 105° (*Komppa* and *Roschier*, Ann. **470**, 140), and α-*fenchocamphorone* (*apocamphor*), m.p. (active and *dl*) 110° (*Komppa* and *Hintikka*, Ber. **47**, 936). From the latter and CH_3MgI, tertiary methyl-α-fenchocamphorol is obtained, and on dehydration this is converted back to α-fenchene (*Komppa* and *Beckmann*, Ann. **508**, 205; cf. the corresponding reactions with camphene). With acetic and sulphuric acids isofenchyl acetate (IVb) is formed. The complete synthesis of *dl*-α-fenchene has been carried out from apocamphoric acid (*Komppa*, Ann. **368**, 126), via *dl*-α-fenchocamphorone (*id.*, Ber. **44**, 1536; *Komppa* and *Roschier*, C. 1917 I 751; *Komppa* and *Beckmann*, Ann. **508**, 205).

β-Fenchene (III) (D, *d-* and L, *l-fenchene*, *isofenchene*), b.p. 150·5–153·5°, d_4^{20} 0·8599, is formed by the decomposition of isofenchyl chloride (IVa) with o-toluidine (*Qvist*, Ann. **417**, 314), by the decomposition of isofenchyl methyl xanthate (isofenchylene is also formed, see below), and by heating fenchyl alcohol (I) with $KHSO_4$, together with γ-, δ- and cyclofenchene (*Komppa* and *Roschier*, Ann. **470**, 143). Oxidation of β-fenchene with $KMnO_4$ leads to *hydroxy-β-fenchenic acid*, m.p. (active) 138°, (*dl*) 126°, and ozone gives *β-fenchocamphorone*, m.p. (active) 62–63°, (*dl*) 66°, *semicarbazone* m.p. (*dl*) 195°, (active) 201°. The further oxidation of β-fenchocamphorone with $KMnO_4$ gives cis-*apofenchocamphoric acid*, m.p. (*dl*) 144–145°, (trans) 148°, which has been synthesized (*Short*, J. **1927**, 961; see also p. 320). β-Fenchocamphorone has been used for the synthesis of β-fenchene by a series of reactions similar to those in the case of α-fenchene (*Komppa* and *Roschier*, Ann. Acad. Sci. Fenn. A. 1916, **10**, No. 3, 3; *Komppa* and *Beckmann*, Ann. **503**, 130). *β-Fenchene dibromide*, m.p. (active) 82°, is not identical with α-fenchene dibromide. *Nitrosochloride* m.p. 120°. With acetic and sulphuric acids isofenchyl acetate (IVb) is formed.

γ-Fenchene, *isopinene* (V), b.p. 145–147°, is obtained from fenchyl alcohol and $KHSO_4$ together with other fenchenes (see above). *γ-Fenchene-phenylazide* m.p. 177° (*Alder* and *Stein,* Ann. **501**, 4). Degradation with ozone gives a **ketonic aldehyde,** $C_7H_{12}:(CHO)(COCH_3)$, (*disemicarbazone* m.p. 219°) and the corresponding **ketonic acid,** $C_7H_{12}(COOH)(COCH_3)$ (*semicarbazone* m.p. 221°); the latter can be converted by alkaline hypobromite into trans-*apofenchocamphoric acid,* m.p. 148° (*Komppa* and *Beckmann,* Ann. **503**, 130). Hydration by the Bertram-Walbaum method gives isofenchyl acetate (IVb).

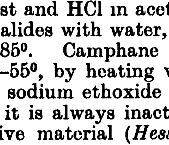
Isofenchylene, δ-fenchene (VI), *iso-allofenchene, isofenchene* (Komppa), *fenchylene* (Nametkin), b.p. 140°/760 mm., d_4^{20} 0·8381, is formed by the dehydration of fenchyl alcohol (I), and by the decomposition of isofenchyl methyl xanthate (*Nametkin* and *Rushenzeva,* C. 1923 I 1501). *Nitrosochloride,* m.p. (*dl*) 131°, (active) 142°. Oxidation with $KMnO_4$ or with ozone gives cis-**isofenchoic acid** (cis-*fenchocamphoric acid*), m.p. (*dl*) 175°, (active) 157·5°, *anhydride* m.p. (*dl*) 92°, (active) 98° (*Qvist,* Ann. **417**, 319; *Nametkin,* J. pr. **106**, 25). The lower homologue, **apoisofenchene,** C_9H_{14}, b.p. 135°/762 mm., obtained from β-fenchocamphoryl chloride by removal of HCl with potassium amyloxide, has a *nitrosochloride* m.p. 145°, and on oxidation with $KMnO_4$ gives cis-apofenchocamphoric acid (see above) (*Komppa* and *Hasselström,* Ann. **497**, 116; **502**, 281).

The saturated hydrocarbons of the *camphane series* can be obtained quite normally: 1. by catalytic hydrogenation of the unsaturated camphane derivatives; 2. by replacement of the halogen atom in halogenated camphane derivatives by H; 3. by decomposition of the hydrazones of the ketones of this series with sodium ethoxide.

Norcamphane, C_7H_{12} (formula, p. 246), m.p. 86–87°, has been prepared from norbornylamine. It is exceedingly volatile and has a peculiar odour, reminiscent neither of the terpenes nor of the petroleum naphthenes (*Komppa* and *Beckmann,* Ann. **512**, 183).

Apocamphane, *7:7-dimethylnorcamphane* C_9H_{16}, m.p. 86°, from α-fenchocamphorone (apocamphor), see *Komppa* and *Hasselström,* Ann. **496**, 168; in the same way, π-apocamphor (santenone) gives **santenane,** *1:7-dimethylnorcamphane,* C_9H_{16}, m.p. 66–67° (*id. ib.* **496**, 170).

Camphane, *1:7:7-trimethylnorcamphane* (*dihydrobornylene, bornylane*),



$C_{10}H_{18}$, m.p. 157–158°, b.p. 159°, sublimes readily. It is formed by the reduction of isobornyl- and bornyl-chloride and -iodide with Na and alcohol, from the iodides with zinc dust and HCl in acetic acid, and by decomposing the Mg compounds of these halides with water, together with a little **hydrodicamphene,** $(C_{10}H_{17})_2$, m.p. 85°. Camphane is formed very easily from camphor hydrazone, m.p. 53–55°, by heating with KOH (*Kishner,* C. 1911 II 363, 1925) or, better, with sodium ethoxide (*Wolff,* Ann. **394**, 86). As it has a symmetrical structure, it is always inactive, no matter whether it is formed from active or inactive material (*Hesse,* Ber. **39**, 1127)[1]. When heated for 30 hours in a sealed tube at 145–150° with nitric acid (1·075), camphane gives two stereoisomeric 2-nitro-compounds: *α-nitrocamphane,* m.p. 128–130°, and α′-, m.p. 146–147°, which are similar in appearance and odour to camphor; both give *dl*-camphor on oxidation with $KMnO_4$ at 0° (*Nametkin*, C. 1916 I 884). The oxidation of camphane with CrO_3 in acetic acid gives epicamphor (*Bredt* and *Pinten*, J. pr. **115**, 48).

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[1] *J. Bredt,* Über die räumliche Konfiguration des Camphers und einiger seiner wichtigsten Derivate, p. 117; Leipzig 1905.

Bornyl chloride (previously known as *pinene hydrochloride*, *Meerwein* and *van Emster*, Ber. **55**, 2501, note 1) (formula IV, p. 267) $C_{10}H_{17}Cl$, m.p. 131°, b.p. 208°, is formed by leading dry HCl into well-cooled pinene, the "true pinene hydrochloride" first formed undergoing rearrangement. It forms a white crystalline mass, which smells of camphor and was once known as "artificial camphor". Bornyl chloride has a rotation in the same direction as the original pinene; values from + 45° to — 34° have been observed. *dl*-Bornyl chloride is obtained from almost inactive American turpentine oil. The constitution of bornyl chloride is shown by the reactions of its Mg-compound $C_{10}H_{17}MgCl$, obtained by the action of Mg in ether; decomposition of this with water gives camphane (p. 273), and the action of oxygen gives chiefly borneol (*Hesse*, Ber. **39**, 1127). Bornyl chloride is quite stable to aqueous alkali, but with energetic reagents such as CaO, alkali phenoxides, and aniline it loses HCl and rearranges to camphene (p. 263). **Bornyl bromide,** m.p. 94°, is obtained from pinene and hydrobromic acid (*Wallach*, Ann. **239**, 7). **Bornyl iodide,** m.p. (active) — 3°, b.p. 99–100°/6 mm., is formed from pinene and hydriodic acid (*Wagner* and *Brickner*, Ber. **32**, 2310), or from bornyl chloride and MgI_2 (*Aschan*, Ber. **45**, 2395). Under certain conditions hydrogen halide can be split out of the bornyl halides without rearrangement to camphene, giving a $\Delta^{2,3}$-compound, bornylene (p. 270) (*Meerwein* and *Joussen*, Ber. **55**, 2529).

Isobornyl chloride, $C_{10}H_{17}Cl$ (formula III, p. 267), m.p. 161·5° (*Meerwein* and *van Emster*, Ber. **55**, 2514, 2527) is formed by the rearrangement of camphene hydrochloride. The presence of a gem-dimethyl group in the bridge is shown by the formation of camphane when its Mg-compound is decomposed with water (*Hesse*, Ber. **39**, 1134). Strong alkali converts isobornyl chloride into camphene, but dilute alkali gives camphene hydrate (p. 279) (*Aschan*, Ann. **410**, 230). For the equilibrium with bornyl chloride on the one hand and with camphene hydrochloride on the other, see *Meerwein* and *van Emster*, Ber. **55**, 2500.

2:6-Dichlorocamphane, *pinene dichloride* $C_{10}H_{16}Cl_2$, m.p. 173–174°, is formed by leading chlorine into dry pinene; it gives tricyclene (cyclene) when treated with sodium (*Aschan*, Ber. **61**, 41; cf. *Brus*, C. r. **180**, 1507).

2:6-Dibromocamphane, *pinene dibromide* $C_{10}H_{16}Br_2$, m.p. 169°, is formed by a similar reaction (*Aschan*, Ber. **61**, 42). Treatment with Zn dust and alcohol gives tricyclene (*Godlevski* and *Wagner*, C. 1897 I 1055), and with sodium and alcohol camphane is formed (*Semmler*, Ber. **33**, 3424).

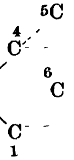
In **ω:2-dibromocamphane** (formula I, p. 264) the two Br atoms have different reactivities. The Br on C_2 can be replaced by OH by treatment with AgOH in acetone, giving ω-bromoborneol, which can be oxidised to ω-bromocamphor (p. 287) (*Qvist*, C. 1930 I 2407).

2:2-Dichlorocamphane, *camphor dichloride*, $C_{10}H_{16}Cl_2$, m.p. 146–148°, is obtained by treating camphor with PCl_5; 2:4-dichlorocamphane and other isomers are formed at the same time (*Meerwein* and *Wortmann*, Ann. **435**, 190; *Houben* and *Pfankuch*, Ann. **489**, 204). Concentrated sulphuric acid converts these dichlorides with varying ease into carvenone (p. 234) (*Bredt*, Ann. **314**, 369).

Isocamphane, *dihydrocamphene*, *2:3:3-trimethylnorcamphane*, m.p. 63°, b.p. 164,5°, is formed by the catalytic hydrogenation of camphene with Pt black (*Lipp*, Ann. **382**, 265), or of tricyclene with Ni at 180–200° (*Meerwein* and *van Emster*, Ber. **53**, 1815). The ω-CH_3 group remains in the endo-position (see p. 277) (*Alder* and *Stein*, Ann. **525**, 203). The nitration of isocamphane gives the same products as those obtained from camphene (*Lipp*, Ann. **382**, 265).

Fenchane, *1:3:3-trimethylnorcamphane*, b.p. 149° (*Nametkin*, C. 1916 II 253) is obtained from fenchone hydrazone m.p. 56–57°, or isofenchone hydrazone, m.p. 111–112° (*Komppa* and *Hasselström*, Ann. **496**, 167), by heating with sodium methoxide, and by the reduction of *d*,α-fenchene dibromide (*Qvist*, Ann. **417**, 323). It has a rotation in the direction opposite to that of the original fenchone or its hydrazone. Nitration gives two nitro-compounds, fenchone, isofenchone and isofenchocamphoric acid (*Nametkin*, C. 1916 II 254). The lower homologue of fenchane, **camphenilane,** *3:3-dimethylnorcamphane* C_9H_{16}, m.p. 15–16°, b.p. 142·6°/753 mm., is formed by the catalytic decomposition of camphenilone hydrazone, m.p. 29–31°, by heating it with caustic potash and platinised porous tile (*Nametkin* and *Shuchrikova*, C. 1916 I 886; *Komppa* and *Hasselstrom*, Ann. **496**, 169). From its two isomeric nitro-compounds (6-nitro- and 2-nitro-camphenilane), β-fenchocamphorone, camphenilone and cis-apofenchocamphoric acid have been obtained (*Nametkin*, Ann. **438**, 185).

Models built up from regular tetrahedra show that in norcamphane the carbon atoms 2 and 6 are close enough to be linked together without undue strain in the molecule, giving a further ring; the formation of this 3-membered ring gives tricyclic compounds:



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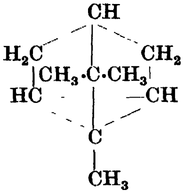

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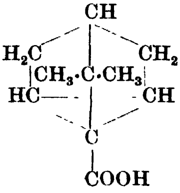

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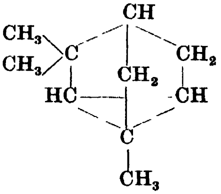

(IV)

These are saturated towards $KMnO_4$, but are attacked by hydrogen halides giving norcamphane derivatives. They can be obtained by removal of halogen from suitable dihalogen-derivatives, by dehydration of norcamphane alcohols, and by the decomposition of diazo-compounds of the norcamphane series.

The first compound of this class known was **tricyclene** (*cyclene*)[1] $C_{10}H_{16}$ (II), m.p. 68°, b.p. 153°, which occurs to the extent of 0·4% in crude camphene from isoborneol, and which remains unattacked after oxidation with $KMnO_4$ (*Moycho* and *Zienkowski*, Ann. **340**, 17). It is identical with the tricyclic hydrocarbon obtained from 2:6-dibromocamphane. Tricyclene is formed with camphene from 2-diazocamphane, which is obtained by the oxidation of camphor hydrazone and decomposes readily (*Vollmann*, Diss., Jena 1915; *Meerwein* and *van Emster*, Ber. **53**, 1815; Germ. Pat. 353,933 (1920); see also *Heubaum* and *Noyes*, Am. **52**, 5070). Tricyclene is very volatile. Addition of acetic acid leads to isobornyl acetate (*Moycho* and *Zienkowski*, Ann. **340**, 25), and HCl gives camphene hydrochloride (*Meerwein* and *van Emster*, Ber. **53**, 1821). **Tricyclenic acid** (III), $C_{10}H_{14}O_2$, m.p. 150°, is obtained by the dehydration of hydroxy-camphenilanic acid (*Lipp*, Ann. **402**, 344), and its carboxyl group can be changed to methyl, via $—CH_2OH$, —CHO, and $—CH{:}N·NH_2$, to give tricyclene (*Lipp*, Ber. **53**, 769; *Komppa*, Ber. **62**, 1366) (p. 269); this proves the structure of the latter. **Teresantalic acid,** $C_{10}H_{14}O_2$ (pp. 270, 333), m.p. 157°, which occurs in nature, has been converted to tricyclene in the same way (*Ruzicka* and *Liebl*, Helv. **9**, 140).

Apocyclene, C_9H_{14}, m.p. 42·4–43°, b.p. 138–139°/748 mm., is formed (1) together with apobornylene, by the dry distillation of camphenilyl methyl xanthate (*Komppa* and *Roschier*, Ann. **429**, 175); (2) from camphenilyl chloride and diethylaniline (*Gratton* and *Simonsen*, J. **1935**, 1621; see also *Lipp* and *Daniels*, Ber. **69**, 586); (3) from camphenilone hydrazone and HgO via the diazo compound (Germ. Pat. 353,933). Hydration gives a mixture of alcohols, since the three-membered ring is opened in all three possible directions; oxidation of this mixture gives chiefly *β*-fenchocamphorone, but small quantities of camphenilone and α-fenchocamphorone are also present (*Nametkin* and *Alexandrov*, Ann. **467**, 191; cf. *Komppa* and *Hasselström*, Ann. **497**, 116). For the addition of HCl to apocyclene, see *Komppa* and *Nyman*, Ber. **69**, 1813. For **phenylapocyclene** see *Bredt-Savelsberg*, Ber. **56**, 554, and for **4-methylcyclene** see *Nametkin* and *Brussov*, J. pr. **135**, 155; *Nametkin* and *Zabrodina*, Ber. **69**, 1789.

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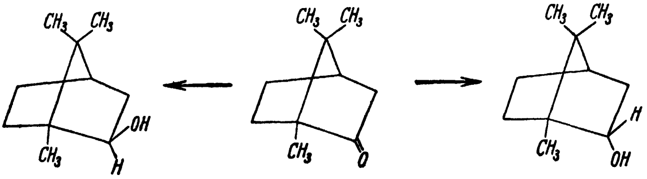
[1] The name is derived from the word cyclo-camphene, used to describe the cyclic isomer of camphene.

Cyclofenchene, *fenchocyclene* (IV, p. 275), b.p. 143·5°/774·5 mm. (*Qvist*, Ann. **417**, 278; *Komppa* and *Roschier*, Ann. **470**, 154; *Nametkin*, J. pr. **106**, 25; *Nametkin* and *Brüssov*, J. pr. **112**, 169), is obtained in a optically active form by the dry distillation of fenchyl methyl xanthate, and is separated from the *l*,α-fenchene also formed by shaking with $KMnO_4$ solution; it is identical with *β-pinolene* (*Aschan*, Ann. **387**, 34). With bromine, *α-fenchene dibromide* is formed, m.p. 86–87°. Hydration by the Bertram-Walbaum method gives the acetates of isofenchyl and fenchyl alcohols. Cyclofenchene can be transformed into α-fenchene via the unstable HCl-addition product, m.p. 26–29°.

Epicyclene, *isocyclene, 3:5-cyclocamphane* (formula II, p. 275), m.p. 117–118°, b.p. 150–152°, is formed from 3:5-cyclocamphanone hydrazone and sodium ethoxide. The optically inactive hydrocarbon is even more volatile than camphane (*Bredt* and *Holz*, J. pr. **95**, 151). For the fission of the 3-membered ring with acetic and sulphuric acids, see *Nametkin* and *Brüssov*, C. 1931 I 269.

2. Alcohols. — The most important alcohols of the norcamphane series are the trimethyl-derivatives, $C_{10}H_{18}O$. Some of these occur in nature, either free or as esters (e.g. borneol and fenchyl alcohol). Two tertiary alcohols, $C_{10}H_{18}O$, prepared in the laboratory, are also important: they are camphene hydrate and the stereoisomeric methylcamphenilol, which can be converted into borneol and isoborneol by way of camphene (see also p. 263). The higher and lower homologues of the secondary and tertiary alcohols, $C_{10}H_{18}O$, have for the most part been obtained synthetically.

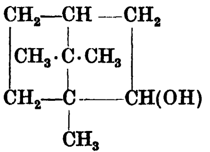
The secondary alcohols, $C_{10}H_{18}O$ are closely related to the ketones, $C_{10}H_{16}O$, to be described later, from which they may be obtained by reduction. According to the conditions (Na and alcohol, H and Pt, etc.), each ketone gives varying quantities of two different alcohols, which show very characteristic differences in their reactivity; their isomerism depends on the position of the OH group relative to the methylene bridge and to the whole molecule. This is shown for the case of the alcohols related to camphor by the following space-formulae:



I II

Formula I, in which the OH group is directed outwards from the bicyclic system, is known as the *exo*-form, according to Bredt, and formula II, in which the OH group is on the inner side, is known as the *endo*-form; this form of isomerism is known as *endo-exo*-isomerism. Bredt has assumed that borneol is the exo-form, and isoborneol the endo-form, because this view seems to give a better explanation of the easy transformation of isoborneol into camphene. Vavon, on the other hand, has found that the esters of cis-methylcyclanols are more difficult to hydrolyse than the esters of the trans-cyclanols, and by a comparison of the rates of hydrolysis of bornyl and isobornyl acetates he concludes that borneol is endo- and isoborneol exo-. This deduction of the configuration of the two camphanols has not been generally accepted (*Lipp*, Ber. **68**, 1029; *Asahina*, *Ishidate* and *Sano*, *ib.* **69**, 343). In the case of the norborneols an absolute proof of the position of the OH group has been obtained (*Alder* and *Stein*, Ann. **514**, 220; p. 321), but this is of no value for the two isomers borneol and isoborneol, for the three methyl groups in the 1:7:7-positions have such a great influence on the properties of the bicyclic system that it is impossible without further evidence to argue from the behaviour of the nor-compounds. Similar relationships hold for the pairs: epi-borneol and epi-isoborneol, α- and β-fenchyl alcohols, methylcamphenilol and camphene hydrate, etc. This *endo-exo*-isomerism is found also with the amines, chlorides and carboxylic acids, in short, whenever a H-atom on carbon atoms 2, 3, 5 or 6 of the norcamphane ring-system is substituted by a univalent residue.

Borneol (I), *Borneo camphor*, *2-hydroxycamphane*, $C_{10}H_{18}O$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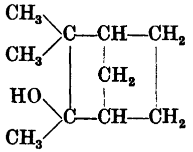
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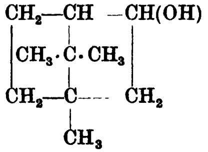

(III)

m.p. 208·5°, (*dl*) 210·3°; b.p. 212°, $[\alpha]_D \pm 37{\cdot}5°$, *phenylurethane* m.p. 139°, *dinitrobenzoate*, m.p. (active) 155°, (*dl*) 152°, occurs naturally in three forms. *d*-Borneol is found in *Dryobalanops camphora*, a a tree growing in Borneo and Sumatra, and in oil of rosemary and other oils, while *l*- and *dl*-borneol are contained in oil of valerian ("valerian camphor") and in the essential oil from *Blumea balsamifera*. Borneol is present in the form of its esters, particularly as its acetate, in many pine needle oils. Pure *l*-borneol can be obtained by the hydrolysis of the *l*-bornyl acetate contained in Siberian pine needle oil. For the preparation of pure *d*- and *l*-borneols from the bornyl esters of bornoxyacetic acid see *Clark* and *Read*, J. **1934**, 1773; for its electric moment see *Harms*, Z. phys. Chem., (B) **30**, 440.

Borneol is very similar to Japan camphor; it sublimes as readily, but is less volatile in steam, crystallises better, and smells not only of camphor but also somewhat of pepper.

Borneol can be prepared artificially in various ways. Reduction of *d*-, *l*- and *dl*-camphor with sodium in alcohol (*Wallach*, Ann. **230**, 225) or in an inert solvent (*Beckmann*, Germ. Pat. 42,458 (1887)) gives borneol and about 20% of isoborneol; the former rotates in the same direction as the starting material, the latter in the opposite direction. In indifferent solvents, more isoborneol is formed than in alcohol, together with about 5% of camphor pinacol, $C_9H_{16}C(OH)\cdot C(OH)\cdot C_9H_{16}$. The action of oxygen on the Mg compound of pinene hydrochloride gives a mixture of borneol and isoborneol, the proportions depending on the temperature of reaction (*Vavon* and *Peignier*, C. r. **181**, 183). Borneol is also formed by heating isoborneol with H_2 under pressure in the presence of catalysts, since it is the more stable form and has the smaller energy content (Germ. Pat. 408,660 (1923)); see also *Barbier* and *Grignard*, Bull. **5** (1909), 512). Borneol is obtained in the form of its esters, together with isoborneol and fenchyl alcohol (cf. *Semmler*, Ätherische Öle III, 442), by heating α- and β-pinenes with organic acids such as acetic, oxalic (*Kawata* and *Tategai*, C. 1933 I 1286; *L. Darrasse*, *E. Darrasse*, *Dupont* and *Elöd*, French Pat. 751,275 [1933]), benzoic, salicylic, chlor- and nitrobenzoic, picric, tetrahalogenated phthalic, etc. (Germ. Pat. 175,097 (1907); 208,487; Brit. Pat. 164,357 (1921); Brit. Pat. 158,533 (1920); U.S.A. Pat. 1,429,342 (1921); *Haller*, C. r. **178**, 1933; *Délépine*, *ib.* **178**, 2087; *id.*, Bull. **35** (1924), 1463; Brit. Pat. 231,468 (1925); French Pat. 592,213 (1924); *Austerweil* and *Petrovici*, Bull. **39** (1926), 1732; Brit. Pat. 258,901 (1926); French Pat. 621,954 (1926); *Austerweil*, Bull. **41** (1927), 1088, 1507; Germ. Pat. 401,870 (1917); Germ. Pat. 406,768 (1917)). For the conversion of pinene into borneol with phosphoboric acid, see Germ. Pat. 582,043 (1931). These methods of preparation of borneol and isoborneol have become important partly for the technical preparation of synthetic camphor. Borneol is oxidised to camphor by chromic acid without any change in the direction of optical rotation. Camphor is obtained in good yield by passing the vapour of borneol over CuO at 300°; Cu effects this dehydrogenation even at 200° (*Masimoto*, C. 1926 I 1643; *Zetzsche* and *Zala*, Helv. **9**, 288; *Hara*, C. 1926 II 2658). Borneol is fairly stable towards dehydrating agents such as dilute sulphuric acid and zinc chloride (*Bertram* and *Walbaum*, J. pr. 49, 8): hence it can easily be separated from isoborneol, which is changed into camphene by this treatment.

Methyl ether, b.p. 194°; *ethyl ether*, b.p. 204° (*Brühl*, Ber. **24**, 3713); the *acetate*, m.p. 29°, b.p. 98°/10 mm., n_D 1·46635, $[\alpha]_D \pm 41{\cdot}55^\circ$, is found in the *l*-form in the oil from *Abies sibirica* (*Golubev*, C. 1905 I 95). *dl*-Bornyl acetate is liquid. The oxidation of bornyl acetate with CrO_3 gives p-keto-bornyl acetate (p. 294), 6-keto-camphor, 6-acetoxy-camphor, and 6-acetoxy-camphorquinone (*Asahina*, *Ishidate* and *Tukamoto*, Ber. **69**, 349).

Bornyl isovalerianate, $C_{10}H_{17}OOC\cdot C_4H_9$, b.p. 255–260°, occurs in oil of valerian; it is used medicinally for nervous complaints under the name of "bornyval". *Bornyl salicylate*, "salite", $C_{10}H_{17}OOC\cdot C_6H_4OH$, m.p. 44–45°, b.p. 171–173°/5 mm., is used in the treatment of neuralgia. Other compounds used medicinally are: *bornyl brom-isovalerianate*, $C_{10}H_{17}OOC\cdot CHBrC_3H_7$, b.p. 113°/10 mm. ("eubornyl", "valisan"); the bornyl ester of *isovalerylglycolic acid* ("neobornyval"), $C_{10}H_{17}OOC\cdot CH_2OOC\cdot C_4H_9$, b.p. 182–183°/12 mm.; and *bornyl dibromcinnamate* ("adamon"), $C_{10}H_{17}OOC\cdot CBr{:}CBr\cdot C_6H_5$, m.p. 65°. *d*- and *l*-Bornyl methyl xanthates give *d*- and *l*-bornylenes (*Tchugaev*, C. 1905 I 94) and camphene (p. 263) when distilled at ordinary pressure. The bornyl halides are identical with the so-called pinene hydrohalides (p. 274).

Isoborneol (formula I, p. 277), $C_{10}H_{17}OH$, m.p. (active) 214°, (*dl*) 212°, $[\alpha]_D$ approx. ± 34°, is stereoisomeric with borneol (*Lipp*, Ann. **480**, 298; *Komppa* and *Beckmann*, Ann. **522**, 137). Its *phenylurethane* has the same m.p., 139°, as that of borneol; *dinitrobenzoate*, m.p. (active) 139°, (*dl*) 131°. For its preparation see under borneol. It is also obtained by the catalytic hydrogenation of camphor with Pt in acetic acid (*Vavon* and *Peignier*, Bull. **39** (1926), 924), and by the hydration of camphene by the method of *Bertram* and *Walbaum* (J. pr. **49**, 1): for the mechanism of this reaction see p. 267. As the conversion of camphene into isoborneol is an important step in the technical preparation of camphor, many attempts have been made to find suitable conditions for this reaction, and many such processes have been patented (e.g. Germ. Pat. 573,797 (1925); U.S.A. Pat. 1,902,364 (1931)). Isoborneol is more volatile than borneol; oxidation with $KMnO_4$, ozone, etc., converts it to camphor with a reversal of the direction of rotation (*Hesse*, Ber. **39**, 1131). When camphene is refluxed with formic acid, it is converted into *isobornyl formate*, b.p. 91—93°/11 mm. (*Semmler* and *Mayer*, Ber. **44**, 2012). *Isobornyl acetate*, b.p. 107°/13 mm., is formed by warming camphene with acetic acid and 50% sulphuric acid to 50—60° (Germ. Pat. 67,255; *Bouchardat* and *Lafont*, C. r. **118**, 248; cf. also Germ. Pat. 184,635 [1905]). Both esters are technically important as intermediates in the preparation of camphor from pinene (p. 286). Isoborneol esterifies more slowly than borneol, and its esters are hydrolysed more slowly (*Vavon* and *Peignier*, Bull. **39** (1926), 924). "Gynoval", used in medicine, is *isobornyl isovalerianate*, $C_{10}H_{17}OOC \cdot C_4H_9$, b.p. 132—133°/13 mm.

An unsaturated isoborneol, **bornylenol, 6-hydroxybornylene,** $C_{10}H_{15}OH$, m.p. 60–61°, b.p. 103–104°/16 mm., is obtained as its acetate by the action of acetic and sulphuric acids upon **isocamphodiene,** *camphenene*, a $\Delta^{5:6}$-camphene, m.p. 41·5–42°, b.p. 149–150°/763 mm. (*Nametkin* and *Zabrodin*, Ber. **61**, 1492).

Camphene hydrate (formula II, p. 277), $C_{10}H_{17}OH$, m.p. 150°, b.p. 205°, *phenylurethane* m.p. 89°, *acetate* b.p. 103–105°, is obtained by digesting camphene hydrochloride with milk of lime (*Aschan*, Ann. **410**, 222). Its smell is musty and also reminiscent of menthol, and it is very readily converted into camphene by dilute mineral acids, and sometimes on distillation (*Aschan*, Ber. **41**, 1092; Ann. **383**, 1). For a camphene hydrate zinc chloride complex, $C_{10}H_{17} \cdot (ZnCl_2OH)$, see *Meerwein*, Ann. **455**, 227.

Methylcamphenilol (formula II, p. 277), $C_{10}H_{17}OH$, m.p. 118°, b.p. 205°, is obtained by the action of MeMgI on camphenilone (p. 268). It is readily dehydrated to camphene by heating with acetic and sulphuric acids (*Moycho* and *Zienkovski*, Ann. **340**, 58). It is stereoisomeric with camphene hydrate. *Acetate*, b.p. 100–102°/11 mm. (*Aschan*, Ann. **410**, 223).

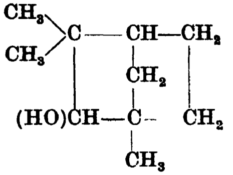
Epiborneol, *3-hydroxycamphane* $C_{10}H_{17}OH$ (formula III, p. 277), m.p. (active) 179°, b.p. 213°, is formed by the reduction of epicamphor (*Bredt* and *Perkin*, jun., J. pr. **89**, 254) or of p-keto-bornyl chloride (*Bredt* and *Pinten*, *ib.* **114**, 52) with sodium and alcohol (see also *Komppa* and *Nyman*, Ber. **69**, 1817). *Phenylurethane* m.p. 79°, *dinitrobenzoate* m.p. 103°. It is oxidised back to epicamphor by chromic acid. Epibornyl xanthate gives pure bornylene on dry distillation.

Epi-isoborneol, $C_{10}H_{17}OH$ (formula III, p. 277), obtained by catalytic reduction of epicamphor with Pt and H_2, has m.p. (active) 195°. *Phenylurethane* m.p. 94–98°, *dinitrobenzoate* m.p. 120°. With alkalis it rearranges to epiborneol much more readily than isoborneol to borneol; hence it cannot be obtained by reducing epicamphor with Na and alcohol (*Lipp* and *Bund*, Ber. **68**, 249).

For the primary alcohols of the camphane series, π-borneol and ω-borneol, see p. 292.

Fenchyl alcohol (I), *fenchol* $C_{10}H_{17}OH$, can exist in two stereoisomeric forms, like the reduction products of camphor; these endo- and exo-forms are designated α- and β-, but it is not known which corresponds to which; the

(I)



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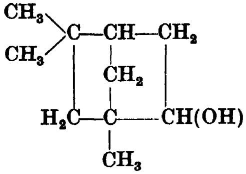

α-form, m.p. (active) 49°, (*dl*) 38°; b.p. 199·5°/750 mm. (*Nametkin*, J. pr. **106**, 25), $[\alpha]_{5461}$ —15·04°, is contained in the oil from the resinous pine-wood of *Pinus palustris*. It is prepared by the reduction of fenchone with Na and alcohol; this gives small quantities of the stereoisomeric β-form, m.p. (active) 5·6°, (*dl*) 6·3°; b.p. 200·5°/750 mm.; $[\alpha]_{5461}$ — 27·97°. This β-form is obtained in better yield by the hydrogenation of fenchone with a very active Ni catalyst (*Schmidt* and *Schulz*, Sch. & Co. Report **1935**, 93). The separation of the two isomers is carried out by means of their hydrogen phthalates and p-nitrobenzoates. α-Fenchol has a fresh smell, reminiscent of camphor, but β-fenchol smells musty and earthy. Both of the *l*-forms correspond to *d*-fenchone, being converted into it by oxidation with CrO_3. Derivatives of α-fenchol: *hydrogen phthalate*, m.p. (active) 145–145·5°, (*dl*) 169°; *phenylurethane*, m.p. (active) 82·5°, (*dl*) 104°; *acetate*, b.p. 88°/10 mm.; the *isovalerianate* is used for the treatment of nervous diseases, under the name "fenchyval" or "valyfen". Derivatives of β-fenchol: *hydrogen phthalate*, m.p. (active) 152°, (*dl*) 153·°; *phenylurethane*, m.p. (active) 89–90°, (*dl*) 90·5°. For the formation of fenchyl alcohol from pinene, see *Semmler*, Ätherische Öle II, 119; *Délépine*, C. r. **179**, 175, 986; *Aschan*, Ann. **387**, 30. The dehydration of fenchyl alcohol gives α-fenchene, a reaction analogous to the formation of camphene from isoborneol, β-, γ-, δ- and cyclo-fenchene (p. 271), and under special conditions (aluminium phosphate at 190°) 1-methylsantene is formed (santene rearrangement) (*Toivonen*, C. 1936 II 3802).

Isofenchyl alcohol, $C_{10}H_{17}OH$ (formula II, above), m.p. 62°, b.p. 98°/13 mm. (*Bertram* and *Helle*, J. pr. **61**, 303; *Nametkin* and *Rushentzeva*, *ib.* **106**, 33; *Qvist*, Ann. **417**, 316), is formed from fenchenes and acetic-sulphuric acids, in the same manner as isoborneol is formed from camphene (see above); on oxidation it gives isofenchone (p. 318), isomeric with fenchone, and cis-isofenchoic acid. *Isofenchyl acetate*, b.p. 97°/12 mm.; *hydrogen phthalate*, m.p. (active) 149–150°; *phenylurethane*, m.p. (active) 106–107°, (*dl*) 94–95° (*Aschan*, Ann. **387**, 44). For fenchyl chlorides from fenchyl and isofenchyl alcohols, see also *Komppa* and *Beckmann*, Ann. **509**, 51.

Camphenilol, $C_9H_{15}OH$, m.p. 84°, b.p. 91·5–92°/11 mm., is formed from camphenilone (p. 319) by reduction with Na and alcohol (*Jagelki*, Ber. **32**, 1499; *Hintikka* and *Komppa*, Ann. **387**, 299): *phenylurethane* m.p. 99·5°, *hydrogen phthalate* m.p. 149°. Reduction of camphenilone in ethereal solution with Na also gives **camphenilone pinacol,** $C_8H_{14}C(OH){\cdot}C(OH){\cdot}C_8H_{14}$, m.p. 134°. Camphenilol and PCl_5 give *camphenilyl chloride*, m.p. 50°, which on boiling with aniline yields santene (*Komppa* and *Nyman*, Ber. **69**, 1813); this is also obtained by the dehydration of camphenilol with P_2O_5 (*Hintikka* and *Komppa*, Ann. **387**, 302). The distillation of camphenilyl methyl xanthate, however, gives apobornylene and apocyclene (*Komppa*, Ann. **429**, 181). For **santenol** and **apoborneol,** see the corresponding ketones, santenone and apocamphor.

Thioborneol, $C_{10}H_{17}SH$, m.p. 120°, is formed by the action of sulphur on bornyl magnesium chloride, by the reduction of **hydropinene-sulphinic acid,** *camphane-sulphinic acid* $C_{10}H_{17}SO_2H$, m.p. 64°, obtained by the action of

SO_2 upon bornyl magnesium chloride, and from thiocamphor by the action of Zn and HCl. Alcoholic iodine oxidises thioborneol to **dibornyl disulphide,** $(C_{10}H_{17})_2S_2$, m.p. 198°, which is decomposed by distillation at ordinary pressures into thioborneol and thiocamphor (p. 288) (*Houben* and *Doescher*, Ber. **39**, 3503; *Sen*, J. Ind. Chem. Soc. **12**, 647).

3. Amines are obtained by reduction of the oximes, and by the action of ammonium formate upon the ketones.

Bornylamine, *2-aminocamphane* $C_{10}H_{17}NH_2$; its formyl compound is prepared by heating camphor with ammonium formate, and the base itself is obtained by the reduction of camphoroxime with Na and alcohol. In the latter reaction, two stereoisomeric optically active bases are formed: *bornylamine,* m.p. 163°, $[\alpha]_D + 47{\cdot}22°$ (*Frankland* and *Barrow*, J. **95**, 2017, 2026), and *isobornylamine,* m.p. 184°, $[\alpha]_D - 43{\cdot}7°$ (*Forster* and *Hart-Smith,* J. **77**, 1152). Bornylamine has a smell similar to that of both camphor and piperidine. Both bases are decomposed by acetic anhydride at 200–210°, giving camphene. For the reaction with nitrous acid, see *W. Hückel* and *Nerdel,* Ann. **528**, 57. **Phenyl-isobornylamine,** $C_{10}H_{17}NH{\cdot}C_6H_5$, b.p. 173–175°/14 mm., *acetyl compound* m.p. 123°, from bornyl chloride and aniline, also by the addition of aniline to camphor, and by the catalytic reduction of camphor-anil (*Lipp* and *Stutzinger*, Ber. **65**, 241); it is reconverted into the latter compound by dehydrogenation (*Ritter*, Am. **55**, 3322). Camphor can be prepared synthetically by means of these reactions (*Ritter*, U.S.A. Pat. 1,987,750 [1933]).

Camphene amine, $C_{10}H_{15}NH_2$, b.p. 161°/200 mm., d^{20} 0·9399, is obtained by loss of HCl from chlorcamphene amine, which can be prepared from 3-aminoborneol, $C_{10}H_{16}(OH)(NH_2)$, the reduction product of 3-aminocamphor (p. 292) (*Duden* and *Macintyre*, Ber. **33**, 481); its constitution is not yet known. With nitrous acid it gives an unsaturated tertiary alcohol, $C_{10}H_{15}(OH)$, m.p. 102°, the so-called *β-isocamphor*; this is isomeric with camphor, and very similar in its physical properties (*Duden* and *Macintyre*, Ann. **313**, 59).

2:3-Diaminocamphane, $C_{10}H_{16}(NH_2)_2$, α-form, b.p. 132–136°/12 mm. (not sterically pure); *β*-form, m.p. 148–149°, is formed by the reduction of camphor quinone dioxime (p. 290) or of aminocamphor oxime (*Duden*, Germ. Pat. 160,103 [1903]). Four diastereoisomeric forms are possible (*Rupe* and *Bohny*, Helv. **19**, 1305).

Camphenilylamine, $C_9H_{15}NH_2$, m.p. 91°, b.p. 185°, is obtained by the reduction of camphenilone oxime with Na and alcohol (*Komppa*, Ann. **366**, 75).

Fenchylamine, $C_{10}H_{17}NH_2$, b.p. 195°, d^{22} 0·9095, is known in three forms, which are obtained from the corresponding fenchones and ammonium formate, and also by the reduction of the fenchone oximes. **D-l-Fenchylamine**[1], $[\alpha]_D$ —24·89°, from *d*-fenchone; with nitrous acid it gives α-fenchene (p. 271) and *d*-limonene (*Wallach*, Ann. **362**, 177). The optical rotation of a series of derivatives has been investigated: *formyl-*, *acetyl-*, *propionyl-* and *butyryl-fenchylamines* have $[\alpha]_D$ —36·56°, —46·62°, —53·16°, and —53·11° respectively (*Wallach* and *Binz*, Ann. **276**, 317).

4. Ketones.—The most important compounds of this group are the natural products of the composition $C_{10}H_{16}O$, camphor and fenchone, which are similar in behaviour but differ in constitution; camphor plays an important part in industry and medicine. Both ketones contain two dissimilar asymmetric carbon atoms, and hence according to the laws of stereochemistry each should exist in four sterically different forms which should be two pairs of optical antimers. Since, however, the trans-form of the norcamphane ring system is sterically impossible owing to the great strain involved (*Bredt*, J. pr. **121**, 157), only one pair of optical isomers can exist in these cases; hence only one *d*-, one *l*- and one *dl*-camphor are known, and the same is true for fenchone. If a further asymmetric carbon atom is present, as for example when the CO group is reduced to CHOH, then four optical isomers are possible; on reduction, camphor gives *d*-, *l*- and *dl*-borneol, and *l*-, *d*- and *dl*-isoborneol, and fenchone behaves similarly. If the bicyclic system is opened, as in the oxidation of camphor to camphoric acid, then the number of isomers known is that predicted by theory, as in other monocyclic compounds (see p. 304).

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[1] See footnote p. 271.

d-Camphor, Japan camphor (formula, p. 283), $C_{10}H_{16}O$, m.p. 178·5—179°, b.p. 209·1°/759 mm., $[\alpha]_D + 44{\cdot}22^0$ in alcohol (*Beckmann*, Ann. **250**, 352), d^{25} 0·992 (*Klemm*, *Tilk* and *von Müllenheim*, C. 1929 I 488), is contained in numerous essential oils, especially the oil from the camphor tree, *Cinnamomum camphora*; it is obtained in large quantities in Japan and Formosa by distillation of the comminuted trunks in steam, and by sublimation. It can be prepared technically, chiefly in the *dl*-form, from oil of turpentine (pinene) by conversion into borneol or isoborneol (pp. 277, 286) followed by oxidation. Camphor is also obtained by the oxidation of camphene with chromic acid, via the intermediate isoborneol which is not isolated. It forms a colourless, transparent, somewhat sticky substance, which can be crystallised from conc. alcoholic solution, and sublimes readily in shining crystals. For its Raman spectrum, see *Bonino* and *Manzoni-Ansidei*, C. 1936 I 1845. It has many therapeutic applications.

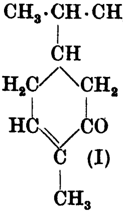
Various preparations of camphor are used for injection in cases of circulatory and respiratory diseases (*Weigert*, C. 1926 II 790, 1882): *Oleum camphoratum*, 10—20% solution of camphor in olive oil; *Ringer's camphor solution*, a solution of camphor in *Ringer's* solution, 1:577; "*cadechol*", a molecular compound of camphor and desoxycholic acid, $(C_{24}H_{40}O_4)_2 \cdot C_{10}H_{16}O$ (*Böhm* and *Nonnenbruch*, C. 1920 III 425; *Rheinboldt*, *Konig* and *Flume*, Z. physiol. Chem. **184**, 219); "*camphocol*", a molecular compound of apocholic acid and camphor, $C_{24}H_{38}O_4 \cdot C_{10}H_{16}O$, m.p. 178—180° (*Bödecker*, Ber. **53**, 1860); "*camphorsol*", a 3% aqueous colloidal solution of camphor with lecithin as a dispersing agent; "*Hochst*" solution of camphor, a 10—20% solution of *dl*-camphor in glycerin diethyl ether (see also C. 1930 I 256); "*camphogen Ingelheim*", an aqueous solution of 2% camphor, 25% diethyl acetamide and 15% Na salicylate. Camphor is used as a disinfectant for external use in numerous preparations, e.g. in phenolcamphor, a molecular compound of phenol and camphor, $C_{10}H_{16}O \cdot C_6H_6O$, solidifying at —18·6°, b.p. 92°/14 mm. (*Bredt*, *Rochussen* and *Monheim*, Ann. **314**, 378); in "*Chlumsky's phenolcamphor solution*" (*Kremann*, *Wischo* and *Paul*, Mo. **36**, 911); in "*isapogen*", a liquid soap containing 6% of iodine and 6% of camphor; and also as a liniment for rheumatism, lameness, etc., in "*Linimentum saponato-camphoratum*" (*opodeldoc*). For *camphor tetrazole*, m.p. 242—243°, see *Knoll* and *Schmidt*, Germ. Pat. 606,615 [1933].)

As *d*-, *l*- and *dl*-camphor have been shown to be pharmacologically equivalent (*Gomes da Costa*, C. 1926 II 1300; *Joachimoglu* and *Klissiunis*, C. 1932 I 1393; *Joachimoglu*, Arch. exp. Pharm. Pathol. **80**, 259, 282), the camphor synthesised commercially has been included in the pharmacopoeias. For the changes undergone by camphor in the animal organism, see hydroxy-camphor, p. 291. The celluloid industry uses large quantities of technical camphor; it is also used in the preparation of smokeless powder (*Du Pont*, Chem. Met. Eng. **26**, 65; *Schmitt*, C. 1923 II 539), and in the manufacture of sulphuryl chloride (*Durrans*, Ch. and Ind. **45**, 347T; *Ishikawa* and *Hashimoto*, C. 1936 I 3127). For the use of camphor as a solvent in molecular weight determinations, see I, 20; cf. the high molecular melting point depressions of camphane, bornylene, etc. (*Pirsch*, Ber. **66**, 1694). Camphor gives p-cymene when distilled with P_2O_5 (vol. III); boiling with iodine yields carvacrol, $C_{10}H_{14}O$ (vol. III), and heating with conc. sulphuric acid to 105—110° gives carvenone (p. 234) and 1:3:4-acetyl-xylene. Boiling with nitric acid gives two acids, *d*-camphoric and camphoronic acids, and reduction gives borneol and isoborneol (pp. 277, 278).

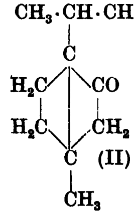
***l*-Camphor, Matricaria camphor,** is found in the oil of *Matricaria parthenium*, and has numerically the same rotation as *d*-camphor: $[\alpha]_D$ — 44·22°. It is formed in the oxidation of *l*-borneol and of *d*-isoborneol, and gives *l*-camphoric acid on oxidation. For the change from *d*- to *l*-camphor, see pp. 293, 300.

***dl*-Camphor,** m.p. 178·5°, is formed by mixing *d*- and *l*-camphor, and by the oxidation of *dl*-borneol, *dl*-isoborneol and *dl*-camphene with chromic acid (*Armstrong* and *Tilden*, Ber. **12**, 1756); it can also be obtained by the racemisation of ordinary camphor with aluminium chloride (*Debierne*, C. r. **128**, 1110). For its technical preparation, see p. 286.

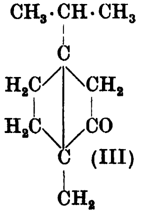
Constitution of Camphor. — *Kekulé's* formula for camphor (I), proposed in 1873, accounted satisfactorily for the conversion camphor into p-cymene and carvacrol; but the ease with which camphoric acid forms its anhydride, which according to (I) would contain a seven-membered ring, did not agree with what was known about the anhydride-formation of aliphatic dicarboxylic acids. The lack of unsaturation in camphor was also inexplicable on this formula. These facts were explained better by the formulae proposed by *Kanonnikov* (II) in 1883, and by *Bredt* (III) in 1884 (*Bredt*, Ber. **26**, 3047), in which the para-carbon atoms of the six-membered ring were linked together. On these formulae, the formation of camphoric anhydride was parallel to that of the anhydride of cyclobutane-1,2-dicarboxylic acid (*Bredt*, Ann. **226**, 261), and offered no difficulty. The CO group was placed in position 2 in formula III because camphor can be converted into carvacrol. *Baeyer* and *Villiger* showed in 1893 that camphoric anhydride probably contained a glutaric anhydride ring, since it melts at a *higher* temperature than the acid (Ann. **276**, 265).



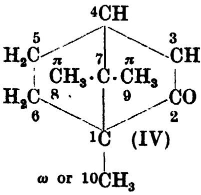
Kekulé 1873



Kanonnikov 1883

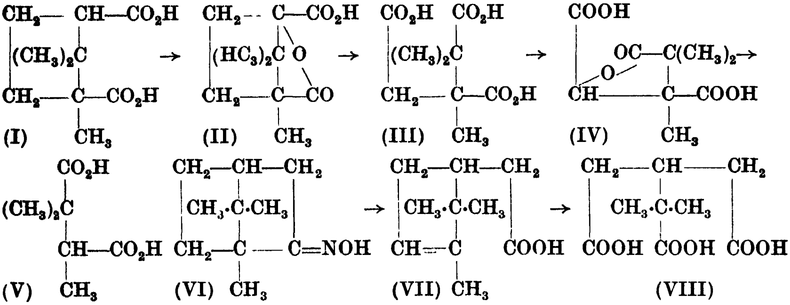


Bredt 1884



Bredt 1893.

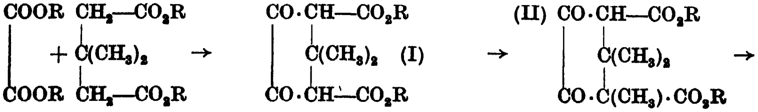
Camphoric acid (I, below) is not the only oxidation product of camphor; further oxidation gives camphanic acid (II) and camphoronic acid (III) (*Bredt*, Ann. **292**, 56). Camphoronic acid (p. 314) was shown by Bredt to be *ααβ*-trimethyl-tricarballylic acid (Ber. **26**, 3049), since on heating it decomposed to give trimethyl-succinic anhydride, isobutyric acid, carbon dioxide, water and carbon, while its further oxidation product, camphoranic acid (IV), the lactone of hydroxy-camphoronic acid, gave trimethyl-succinic acid (V) and oxalic acid smoothly on fusion with potash (*Bredt*, Ann. **299**, 140). Trimethyl-succinic acid has also been found amongst the oxidation products of camphor (*Bredt*, Ber. **27**, 2094). Camphor can be degraded in yet another direction: the dehydration of camphor oxime (VI) yields α-campholenic nitrile, which can be hydrolysed to α-campholenic acid (VII); oxidation of this with chromic acid gives isocamphoronic acid (VIII) (*Bredt*, Ber. **26**, 3055; Ann. **314**, 395).

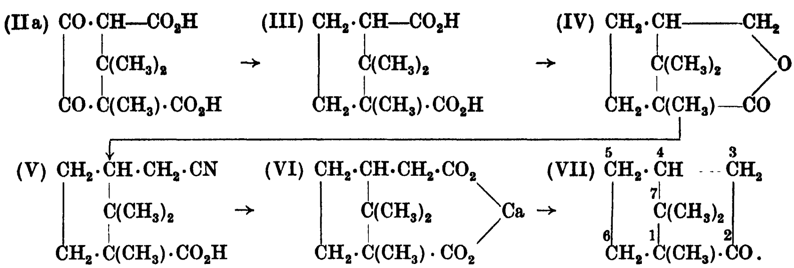


As a result of these two degradations of camphor in different directions, *Bredt* in 1893 proposed formula (IV p. 283) for camphor, with a dimethyl-methylene bridge in the 1:4-position. Other constitutional formulae, such as those of *Wagner* (Ann. **292**, 129), *Tiemann* (Ber. **28**, 1089), *Bredt* (Ann. **289**, 15), *Perkin, jun.* (J. **78**, 819), and *Bouveault* (C. 1897 II 856), have not stood the test of further investigation. On the basis of the above constitutional formulae, *Perkin jun.* and *Thorpe* were able synthesise camphoronic and isocamphoronic acids (*Perkin jun.*, Proc. **16**, 214).

The final proof of *Bredt's* constitutional formula was given by the synthesis of camphor, which was carried out in two stages, viz., (1) the synthesis of camphoric acid; and (2) the conversion of camphoric acid into camphor. The second stage of the synthesis was completed first. *Bredt* and *v. Rosenberg* obtained *d*-camphor (VII below) in 70% yield by distilling the Ca-salt of homocamphoric acid (VI), and concluded from this that homocamphoric acid was a substituted adipic acid (Ann. **289**, 5). *Haller* carried out the same synthesis with the lead salt of homocamphoric acid (C. r. **122**, 446), but inferred that this acid belonged to the glutaric acid series; he obtained the nitrile (V) of homocamphoric acid from camphoric acid by reduction of its anhydride to campholide (IV), and treatment of this with KCN (cf. *Ruzicka* and *Kuhn*, Helv. **8**, 752). *Blanc* cyclised homocamphoric acid to camphor with acetic anhydride (C. r. **144**, 1357).

The first synthesis of camphoric acid was carried out by *Komppa* (Ann. **370**, 209): oxalic ester and *ββ*-dimethylglutaric ester were condensed with sodium ethoxide to give the ester of diketo-apocamphoric acid (I); methylation of this with methyl iodide and sodium in alcoholic solution yielded the ester of diketocamphoric acid (II); this acid (IIa) was reduced to a mixture of cis- and trans- *dl*-camphoric acids (III), by way of dihydroxy-, dehydro- and bromo-camphoric acids:

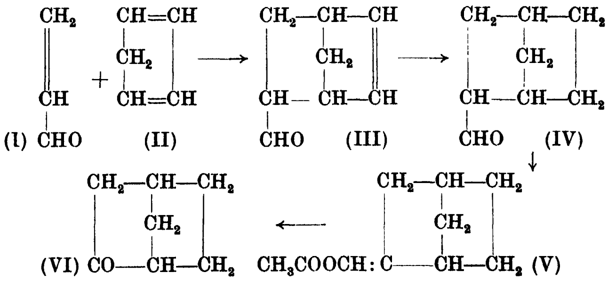




dl-Camphoric acid can be resolved by means of its cinchonidine salt into *d*- and *l*-camphoric acids, and hence a synthesis of optically active camphor can be realised. *Bredt's* formula for camphor solved a problem which had occupied the minds of many investigators since the time of *Berthelot* (1859).

For other syntheses of camphoric acid, by *Perkin jun.* and *Thorpe* (J. **89**, 795) and by *Toivonen* (C. 1927 II 1248), see p. 304. For stereochemical considerations with regard to the camphor molecule, cf. *Aschan*, Ann. **316**, 209, and *Bredt*, J. pr. **121**, 157. For the formation of camphor from campholenic acid, see *Lipp* and *Lausberg* (Ann. **486**, 278); from benzylidene-campholic acid chloride, see *Rupe* and *Sulger* (Helv. **6**, 259), and *Haller* and *Palfray* (C. r. **178**, 1647). The reaction-mechanism of the change from linalool to camphor is still unexplained (*Vinogradova*, Ber. **64**, 1991).

In the *Bredt-Haller-Komppa* synthesis of camphor, the 5-membered ring with the three methyl groups, consisting of C-atoms 1, 7, 4, 5, 6, is first built up, and this is followed by closure of the second 5-membered ring containing atoms 1, 2, 3, 4, 7. The synthesis of camphor by *Diels*, however, starts with one 5-membered ring already formed: acrolein (I) is condensed with cyclopentadiene (II) to give the bicyclic system of norcamphane in the form of Δ^5-norbornylene-2-aldehyde (III); the methyl group is introduced later. The norbornylene-2-aldehyde is reduced to norcamphane-2-aldehyde (IV), the enol acetate (V) of which gives norcamphor (VI), m.p. 94°, on ozonisation (*Diels* and *Alder*, Ann. **460**, 105; **470**, 62); this compound can also be obtained from the Pb-salt of homonorcamphoric acid (*Hintikka* and *Komppa*, Ann. Ac. Scient. Fenn. A, **10**, No. 22). The synthesis is completed via the compounds: camphenilone, methyl-camphenilol, camphene and camphor (*Diels*, *Alder*, Ann. **486**, 202).



The formulae for borneol, camphene and many other compounds related to camphor can be derived from formula (IV) (p. 283) for camphor. It is frequently difficult to understand the relationship between camphor and its reaction products, because of the profound molecular rearrangements these may undergo, particularly under the influence of acid reagents (cf. β-campholenic acid and β-campholytic acid, etc.).

The technical preparation of camphor has a long history. The following observations were its basis: in 1841, *Pelouze* obtained camphor from Borneo camphor (borneol) by oxidation; in 1858, *Berthelot* prepared camphene as a solid from pinene hydrochloride, and in 1869 he was able to oxidise this to camphor with chromic acid; *Lafont* obtained isobornyl formate by the action of formic acid upon camphene, and acetic acid was added on in the same way when the reaction was carried out at 100° for 60 hours; *Bertram* and *Walbaum* found that this reaction was accelerated by addition of sulphuric acid. The addition of water to pinene with the formation of borneol was also known quite early: *Bouchardat* and *Lafont* were able to carry out this hydration by the action of conc. sulphuric acid, benzoic acid or formic acid upon pinene (C. r. **113**, 551). The inducement to utilise these observations for the technical synthesis of camphor was given by the increasing use of camphor in industry (see above), and by the Japanese monopoly.

The processes used fall into three groups; the starting material is always pinene, which is available in large quantities in oil of turpentine.

I. Addition of organic acids to pinene to give bornyl esters, and hydrolysis of these to borneol, which is oxidised to camphor. This process is of limited value because of the many by-products formed in the esterification (p. 278).

II. Addition of HCl to pinene to give bornyl chloride, removal of HCl to yield camphene (cf. also *Acharya* and *Wheeler*, J. Univ. Bombay, **3**, 163):

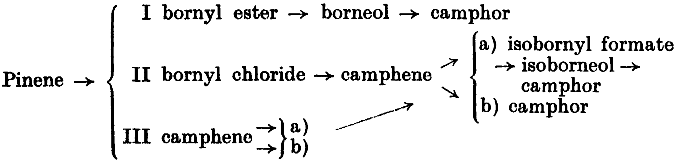
a) formation of isobornyl formate from camphene with formic and sulphuric acids, hydrolysis to isoborneol, and dehydrogenation of this with the aid of metallic oxides such as NiO and CuO in the presence of alkali or alkaline earth (*Schmitz* and *Co.*, Germ. Pat. 203,792 [1907]).

b) direct oxidation of the camphene to camphor with chromic acid.

Process IIa is particularly good, and most synthetic camphor is made this way.

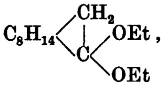
III. Catalytic rearrangement of pinene into camphene and further treatment according to IIa or IIb.

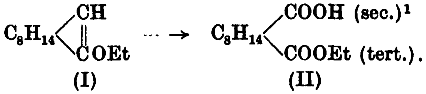
The following table summarises these processes:


Pinene →
I bornyl ester → borneol → camphor
II bornyl chloride → camphene
a) isobornyl formate → isoborneol → camphor
b) camphor
III camphene → a) → b)

Reaction products of Camphor.

Functional derivatives of camphor.

Camphor diethyl acetal, 
$C_8H_{14}\left\langle\begin{array}{l}CH_2\\ |\\ C\left\langle\begin{array}{l}OEt\\ OEt\end{array}\right.\end{array}\right.$, b.p. 102–103°/11·5 mm., is formed from camphor and ethyl orthoformate in alcoholic solution, in the presence of mineral acid as catalyst; with P_2O_5 in pyridine it loses alcohol, giving **camphor enol ethyl ether** (I), b.p. 73·7–74·6°/11 mm. The constitution of this very unstable substance is shown by its conversion into the tertiary mono-ethyl ester of camphoric acid (II) (*Bredt-Savelsberg* and *Rumscheidt*, J. pr. **115**, 235):



$$C_8H_{14}\left\langle\begin{array}{l}CH\\ \|\\ C\,OEt\end{array}\right. \dashrightarrow C_8H_{14}\left\langle\begin{array}{l}COOH\ (\text{sec.})^1\\ COOEt\ (\text{tert.}).\end{array}\right.$$

(I) (II)

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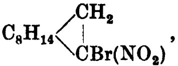
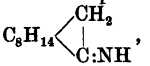
[1] For the meaning of these terms see p. 306.

Camphor oxime, $C_{10}H_{16}{:}NOH$, m.p. (active) 119°, (*dl*) 118°, b.p. 249° (*Wallach*, Ann. **259**, 331; *Bredt* and *v. Rosenberg*, Ann. **289**, 6), gives bornylamine and isobornylamine on reduction. Potassium hypobromite converts it into *2-brom-2-nitrocamphane*,  $C_8H_{14}\left\langle\begin{array}{l}CH_2\\ \mid\\ CBr(NO_2)\end{array}\right.$, m.p. 220° (*Ginnings* and *Noyes*, Am. **44**, 2567), which on reduction gives *2-nitrocamphane*, $C_{10}H_{17}NO_2$, m.p. (active) 148°, aci-form (active) 74°. For nitro-compounds formed by the nitration of camphane, see *Nametkin*, C. 1916 I 884. The action of nitrous acid on camphor oxime yields the nitrate of **2-iminocamphane,** *α-camphorimine*  $C_8H_{14}\left\langle\begin{array}{l}CH_2\\ \mid\\ C{:}NH\end{array}\right.$, m.p. 95°, together with a substance $C_{10}H_{16}O_2N_2$, m.p. 43°, known as *pernitrosocamphor* or *camphor nitrimine*; treatment of the latter with sulphuric acid gives *3-isopropyl-1-acetyl-*Δ^1*-cyclopentene* (*isocamphor*), a ketone isomeric with camphor (p. 61). **Camphor anil,** $C_{10}H_{16}{:}N{\cdot}C_6H_5$, m.p. 13·5°, b.p. 164·5–166°/15 mm., is obtained from camphor and aniline, or from N-phenyl-isobornylamine by dehydrogenation (p. 281). Camphor oxime and **camphor phenylhydrazone,** b.p. 210°/17 mm., can be prepared easily from thiocamphor (p. 288) (*Wuyts*, Ber. **36**, 868; *Sen*, C. 1936 I 4916). **Camphor semicarbazone,** m.p. (active) 247–248°, (*dl*) 234° (*Bredt* and *Perkin jun.*, J. pr. **89**, 240). **Camphor phenylsemicarbazone,** m.p. (active) 153–154°, (*dl*) 171·5–172·5° (*Morani*, Gazz. **58**, 409). **Camphor hydrazone,** m.p. 55°, gives camphane by heating with sodium methoxide (*Wolff*, Ann. **394**, 86).

Substitution products of Camphor.[1]

Halogen substitution products. — By the action of chlorine and bromine on camphor, or by loss of CO_2 from halogen-camphocarboxylic acids, the following compounds are obtained: **3-Chlorcamphor** (α-chlorcamphor), m.p. (active) 94°, and **3-bromcamphor** (α-bromcamphor), m.p. (active) 76°, (*dl*) 51° (*Ingersoll* and *Babcock*, Am. **55**, 341). **3-Iodocamphor,** m.p. (active) 44°, is formed from Na-camphor and iodine, or from 3-bromcamphor and Mg and iodine. Treatment of 3-chlorcamphor with a little NaOEt gives the stereoisomeric **3′-chlorcamphor,** m.p. (active) 117°; nitration of this yields **3-nitro-3′-chlorcamphor,** m.p. (active) 132°, while 3-chlorcamphor gives **3′-nitro-3-chlorcamphor,** m.p. 95° (*Lowry* and *Steele*, J. **107**, 1382). Similarly, 3-bromcamphor gives **3′-bromcamphor,** m.p. (active) 78° (*Lowry*, *Steele* and *Burgess*, J. **121**, 633). The action of Na on bromcamphor gives *dicamphor*, $(C_{10}H_{15}O)_2$, and *dicamphene-dione*, $(C_{10}H_{14}O)_2$ (see Germ. Pat. 94,498 (1896); *Oddo*, Ber. **37**, 1569). α-Bromcamphor and Mg in ether give *camphor magnesium bromide*, which has been found of use in synthetic work (*Malmgren*, Ber. **36**, 2608; *Bruhl*, *ib.* **37**, 749). **ω-Bromcamphor**[2] (previously β-bromcamphor), m.p. (active) 79°, is formed from camphor sulphobromide (see below) by the action of heat (*Bredt* and *Pinten*, J. pr. **119**, 88; *Qvist*, C. 1930 I 2407), or from hydroxy-camphene and bromine in acetic acid. **ω-Bromcamphor-α-sulphonic acid** is formed from **ω-bromcamphor** and sulphuric acid in acetic anhydride (*Burgess* and *Lowry*, J. **127**, 271). **π-Bromcamphor**[2] exists in a stable and a labile form, m.ps. (active) 93·4° and 63° respectively; it is formed by heating π-camphorsulphonic acid bromide. para-**Bromcamphor,** *2-keto-5-bromcamphane*, can be obtained by the addition of HBr to 3:5-cyclocamphanone (*Bredt* and *Holz*, J. pr. **95**, 138). **3:3′-Dibromcamphor,** m.p. 61°, is formed by the further bromination of 3-bromcamphor (*Burgess* and *Lowry*, J. **123**, 1867); for its degradation with fuming nitric acid, see *Lapworth*, J. **75**, 1134. **3:ω-Dibromcamphor,** m.p. 115°, is formed by heating 3:3′-dibromcamphor for some time (*Bredt* and *Pinten*, J. pr. **119**, 88; *Loudon*, J. **1935**, 535). **3:3′-Di-iodo-**

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[1] The system of showing the position of substituents is shown in the formula for camphor on page 283.

[2] For the meaning of ω and π, see formula for camphor, p. 283.

camphor, m.p. 109°, is formed by the action of iodine on an alkaline alcoholic solution of iodo-formyl-camphor (*Bruhl*, Ber. **37**, 2156).

The action of PCl_5 on camphor gives **camphor dichloride,** *2:2-dichlor-camphane*, and various isomers (p. 274).

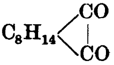
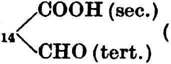
The action of hot nitric acid on 3-chlorcamphor and 3-bromcamphor gives 3-chlor-3′-nitrocamphor (see above) and 3-brom-3′-nitrocamphor respectively, which can be reduced with Cu-Zn or by treatment with sodium methoxide to **3′-nitrocamphor,** m.p. (active) 102° (*Cazeneuve*, C. r. **108**, 243, 302; id., Bull. **2** (1889), 706; *Pescetta*, Gazz. **25**, II 418; *Bruhl*, Ber. **37**, 2077; *Lowry* and *Steele*, J. **107**, 1038); this can be converted into the *aci*-form, which gives characteristic salts. The reduction of nitrocamphor yields aminocamphor (p. 292). For **p-chlor-** and **p-brom-epicamphor,** see under epicamphor (p. 293).

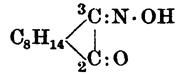
Camphor and hot alcoholic ammonium sulphide gives a mixture of sulphides, from which **thiocamphor,** $C_{10}H_{16}S$, red needles of m.p. 145°, b.p. 104°/15 mm., and thioborneol (p. 280) can be obtained by distillation (*Wuyts*, Ber. **36**, 863). Pure thiocamphor is prepared from an alcoholic solution of camphor with HCl and H_2S at 0°. Its smell is like that of camphor; it can be converted into the *isonitroso-compound*, violet needles of m.p. 148°, the sensitivity of which towards alkali makes it suitable as an indicator (*Rây*, Nature **134**, 1010; *Sen*, C. 1936 I 4015; II 1354).

Camphorsulphonic acids. — The treatment of camphor with fuming sulphuric acid or with chlorsulphonic acid yields **dl-camphor-π-sulphonic acid,** m.p. 56–58°; its compound with diethylene diamine is known as "*solu-camphor*" (*Regniers* and *Vleeschhouwer*, C. 1935 II 2237); with conc. sulphuric acid and acetic anhydride, **camphor-ω-sulphonic acid** (*Reychler*'s camphorsulphonic acid), m.p. (active) 193°, (*dl*) 202°, is formed (*Lipp* and *Lausberg*, Ann. **436**, 275; *Frèrejacque*, C. r. **196**, 1513; *Loudon*, J. **1933**, 823; *Sillani* and *Curti*, C. 1935 I 3955). *d*-Camphor-π-sulphonic acid (from *d*,3-bromcamphor-π-sulphonic acid by reduction), and particularly *d, 3-brom-camphor-π-sulphonic acid*, m.p. 195–196° (from *d*, 3-bromcamphor and fuming sulphuric acid: *Regler* and *Hein*, J. pr. **148**, 1), are frequently used for the resolution of racemic bases (e.g. *Pope* and *Peachey*, J. **77**, 1072; *Wedekind* and *Frohlich*, Ber. **39**, 4439). Fusion of the ω-sulphonic acid with potash breaks one of the rings to give α-campholenic acid. Reduction of the ω-sulphonic acid, followed by dehydration, leads to the sultone, *2-hydroxy-camphane-ω-sulphonic acid lactone*, m.p. 133·5° (*Lipp* and *Holl*, Ber. **62**, 499), which can also be obtained from camphene and SO_3 in acetic acid. For sultams, see *Screiber* and *Shriner*, Am. **57**, 1896. The *methyl ester* of *camphor-3-sulphonic acid*, m.p. 77°, is formed by the action of $Cl \cdot SO_2 \cdot OCH_3$ ("vaillantite") on camphor; it corresponds to the camphocarboxylic esters, and like these it is soluble in alkali (*Frèrejacque*, C. r. **183**, 607).

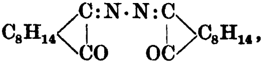
Keto-derivatives of camphor. — **p-Ketocamphor,** *2:5-diketocamphane*, m.p. 210°, $[\alpha]_D + 103{\cdot}42°$, in ethyl alcohol; solubility in water at 18° = 2·191%, is formed by the oxidation of camphor with chromic acid in acetic acid (*Bredt*, J. pr. **106**, 342), and by treatment of p-keto-borneol and of p-hydroxy-camphor (see below) with CrO_3 (*Bredt* and *Goeb*, J. pr. **101**, 288). Its pharmacological action is similar to that of camphor. *Disemicarbazone* m.p. 290°. (*Asahina* and *Ishidate*, Ber. **67**, 73); this gives camphane when heated with sodium ethoxide in a sealed tube. The *mono-semicarbazone*, m.p. 240°, is converted into borneol by this reaction, the free CO group being reduced; this shows that it is the 5-mono-semicarbazone (id., ib.). p-Keto-camphor readily forms mono- and dibromo compounds with bromine (*Bredt* and *Pinten*, J. pr. **119**, 102), and with Na and CO_2 it gives *2:5-diketo-camphane-6-carboxylic acid*, m.p. (active) 210–211° (*Asahina* and *Ishidate*, Ber. **67**, 440). In the animal organism, p-diketocamphane gives 4-hydroxydiketocamphane and a π-hydroxy-compound; the latter, by oxidation with CrO_3, gives **apo-cyclo-camphanone-7-carboxylic acid,** $C_{10}H_{12}O_3$, m.p. 248–250°, also obtained from cyclocamphanone and CrO_3 (*Reindrtz*, *Zanke* and *Faust*, Ber. **67**, 1537).

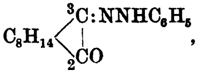
6-Keto-camphor, *2:6-diketo-camphane* $C_{10}H_{14}O_2$, m.p. 189–190°, *dioxime* m.p. 244–245°, *disemicarbazone* m.p. 290° (decomp.), is formed by the dehydration of dihydroxy-dihydro-α-campholenic acid, and from α-campholonic acid (p. 301); it can also be obtained, together with other products, by the oxidation of bornyl acetate with CrO_3 (p. 278) (*Asahina, Ishidate* and *Tukamoto,* Ber. **69**, 349).

Camphor quinone, *2:3-diketocamphane*  $C_8H_{14}\left<\begin{array}{l}CO\\ |\\ CO\end{array}\right.$, m.p. 198°, is formed from isonitroso-camphor by treatment with sodium bisulphite or formaldehyde, by the oxidation of camphocarboxylic acid (*Aschan,* Ber. **27**, 1447), and by the oxidation of camphor with SeO_2 in acetic anhydride (*Evans, Ridgion* and *Simonsen,* J. **1934**, 137). It is similar to the quinones, has a characteristic sweetish smell, is volatile in steam and sublimes at 59–60° in golden-yellow needles (*Claisen* and *Manasse,* Ann. **274**, 71). Fusion with alkali gives the **semi-aldehyde of camphoric acid,**  $C_8H_{14}\left<\begin{array}{l}COOH\ (sec.)\\ CHO\ (tert.)\end{array}\right.$ (*Bredt,* J. pr. **96**, 65). Oxidation of camphor quinone yields camphoric acid itself. The opening of the ring between C_2 and C_3 takes place so readily that an ethereal solution of camphor quinone gives camphoric anhydride merely by standing in daylight. Conc. sulphuric acid converts camphor quinone into a ketonic acid, $C_{10}H_{16}O_3$, *2:3:3-trimethylcyclohexanone-4-carboxylic acid,* m.p. (+ H_2O) (active) 67–68° (*Bredt-Savelsberg, Zaunbrecher* and *Knieke,* Ber. **60**, 1803). With moist bromine, camphor quinone yields $C_{10}H_{12}O_3Br_2$, m.p. (active) 137–138°, and $C_{10}H_{11}O_3Br_3$, m.p. (active) 199–200°, both of which are brominated lactones of 2-hydroxy-2-bromomethyl-3:3-dimethylcyclohexanone-4-carboxylic acid; the position of the bromine atoms, with the exception of that on the 2-methyl group, is not known with certainty. The tribromo compound is reduced by Zn dust and acetic acid in the cold to a *monobromo derivative* $C_{10}H_{13}O_3Br$, m.p. (active) 144–145°, but at higher temperatures the ketonic acid above, $C_{10}H_{16}O_3$, is obtained (*Evans, Simonsen* and *Bhagvat,* J. **1934**, 444). Fuming sulphuric acid brings about a rearrangement of camphor quinone even at 0°; the $CH_3\cdot C\cdot CH_3$-bridge (cf. p. 300) is opened to give dehydro-buchu-camphor ("*camphor isoquinone*"; buchu-camphor [p. 237] with two atoms of H less in the molecule), which has been degraded to δδ-dimethyl-δ-hydroxy-laevulinic acid (*Bredt, Rochussen* and *Monheim,* Ann. **314**, 389; *Manasse* and *Samuel,* Ber. **35**, 3834).

Isonitroso-camphor, *camphor quinone 3-monoxime,*  $C_8H_{14}\left<\begin{array}{l}{}^3C{:}N\cdot OH\\ |\\ {}_2C{:}O\end{array}\right.$ exists in a stable (anti-) form, m.p. (active) 153°, and a labile (syn-) form, m.p. (active) 114° (*Forster,* J. **83**, 514; **1926**, 2670; *Meisenheimer* and *Theilacker,* Ann. **493**, 33); it is formed by the action of amyl nitrite and Na or K amide upon camphor in benzene solution (*Bredt,* J. pr. **95**, 65; **121**, 162), and is purified by solution in conc. ammonia and precipitation with CO_2. Concentrated sulphuric acid converts it into camphoric acid imide (*Manasse,* Ber. **26**, 241), PCl_5 gives the acid chloride of camphoric acid semi-nitrile (*Rupe* and *Splittgerber,* Ber. **40**, 4313), and reduction with Zn and dilute acid gives amino-camphor (*Claisen* and *Manasse,* Ann. **274**, 90; cf. camphor quinone).

Camphor quinone monohydrazone is formed by the action of hydrazine hydrate upon camphor, and exists in two forms, m.p. (α) 206°, (β) 102° (*Forster,* J. **97**, 2156); yellow HgO converts it to **3-diazo-camphor** (p. 292).

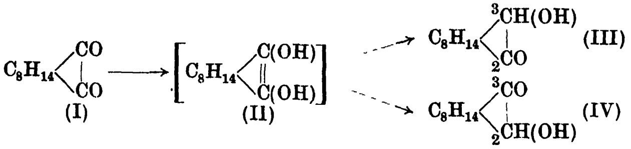
Bis-camphanone-azine, *azocamphenone*  $C_8H_{14}\left<\begin{array}{l}C{:}N\cdot N{:}C\\ |\qquad\quad\ |\\ CO\qquad OC\end{array}\right>C_8H_{14}$, m.p. 222°, occurs as a by-product in the preparation of camphor quinone hydrazone. The interaction of camphor quinone and ketonic reagents leads for the most part to 3-substituted camphor quinone derivatives; but methylamine gives methylimino-epicamphor; this can be reduced to methylamino-epicamphor, which solidifies at 18° (*Rupe* and *Martin*, Helv. **17**, 1207).



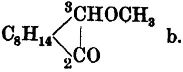
Camphor quinone mono-phenylhydrazone, $C_8H_{14}\left<\begin{matrix}{}^3C{:}NNHC_6H_5\\ |\\ {}_2CO\end{matrix}\right.$, occurs in two geometrically isomeric forms, m.ps. 190° and 36°; for their structure and configurations see *Forster*, J. **99**, 478.

Camphor quinone dioxime: two forms, m.p. (α) 201° and (β) 248°, are formed from isonitroso-camphor and hydroxylamine acetate. The *γ-dioxime*, m.p. 136°, from isonitroso-camphor and free hydroxylamine, changes on melting to the *δ-dioxime*, m.p. 194° (*Forster*, J. **83**, 514; **103**, 662; see also *Meisenheimer* and *Theilacker*, Ann. **493**, 33).

Hydroxy-derivatives of Camphor. — The reduction of camphor quinone gives two hydroxy-camphors III + IV, with different structures; they arise from the rearrangement of a dihydroxy-bornylene (II) which is the first product of the reduction (*Bredt* and *Breat-Savelsberg*, Ber. **62**, 2214):

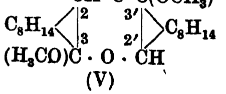


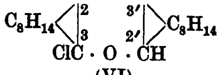
3-Hydroxycamphor, *α-hydroxy-camphor, 2-keto-3-hydroxy-camphane* $C_{10}H_{16}O_2$ (III), m.p. (active) 197–198°, (*dl*) 200°, is the main product of the reduction of camphor quinone with Al amalgam in ether, a reaction in which only a small amount of 2-hydroxy-epicamphor (IV) (see below) is formed. After the removal of the 2-hydroxy-epicamphor as its bimolecular ether (see below), the 3-hydroxy-camphor is purified through its beautifully crystalline *semicarbazone*, m.p. (active) 183–184° (*Bredt*, J. pr. **121**, 165).



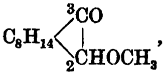
The *methyl ether*, $C_8H_{14}\left<\begin{matrix}{}^3CHOCH_3\\ |\\ {}_2CO\end{matrix}\right.$ b.p. 105–107°/15 mm., is obtained by boiling 3-hydroxy-camphor in methanol in a current of HCl for some time; *semicarbazone*, m.p. 204°. The *acetate*, m.p. 61–62°, has the same m.p. as the isomeric 2-hydroxy-epicamphor acetate, but is not identical with it (*Bredt*, J. pr. **121**, 170). The reduction of 3-hydroxy-camphor with Na amalgam gives ordinary camphor exclusively (*Ishidate*, C. 1928 II 654). For the formation of 3-hydroxy-camphor as a product of metabolism, see under camphorol (p. 291).

2-Hydroxy-epicamphor, *β-hydroxy-camphor, 2-hydroxy-3-keto-camphane* $C_{10}H_{16}O_2$ (IV), m.p. (active) 211°, (*dl*) 212–213°, is obtained as the chief product, accompanied by small amounts of 3-hydroxy-camphor, by the reduction of camphor quinone with Zn dust and acetic acid. It gives a characteristic bimolecular *methyl ether* $C_{22}H_{36}O_4$ (V), m.p. (active) 149–150°, (*dl*) 133–134°, when treated with methyl alcoholic HCl; under these conditions the 3-hydroxy-camphor is unchanged or gives the liquid mono-molecular ether (see above), and hence the method can be used to separate the two compounds. When the OH group in 2-hydroxy-epicamphor is replaced by Cl with thionyl chloride, two molecules condense together during the reaction to give an acetal-like compound, which may be given formula (VI), analogous to the formula (V) for the bimolecular ether:


(V)


(VI)

The bimolecular ether is hydrolysed by conc. HCl in the cold, giving 2-hydroxy-epicamphor, *semicarbazone* m.p. (active and *dl*) 215–216°; treatment with hot methanolic HCl, however, gives the *monomolecular ether*



$C_8H_{14}\left<\begin{array}{l}{}^{3}CO\\ |\\ {}_{2}CHOCH_3\end{array}\right.$, m.p. 37–38°, b.p. 105–106°/12 mm., *semicarbazone* m.p. 124°. 2-Hydroxy-epicamphor *acetate* has m.p. 61–62°, the *benzoate* has m.p. 84–85°. 2-Hydroxy-epicamphor reacts with excess of CH_3MgI with evolution of methane and formation of *3-methyl-2:3-dihydroxy-camphane*, m.p. 163–164°. 2-Hydroxy-epicamphor is unstable towards alkali and undergoes rearrangement into 3-hydroxy-camphor (*Bredt*, J. pr. **131**, 56); hence the action of alkaline reagents upon 2-hydroxy-epicamphor gives derivatives of 3-hydroxy-camphor, as well as those of 2-hydroxy-epicamphor e.g., the reduction of 2-hydroxy-epicamphor with Na amalgam gives chiefly epicamphor (see below) (*Bredt* and *Bredt-Savelsberg*, Ber. **62**, 2214), but some camphor is also formed from the 3-hydroxy-camphor. Under different conditions of reduction (Na and alcohol), both 3-hydroxy-camphor and 2-hydroxy-epicamphor give *2:3-dihydroxycamphane*, m.p. 231° (*Manasse*, Ber. **35**, 3811). Camphor quinone is reduced in the animal organism (by feeding to dogs) to 2-hydroxy-epicamphor, identical with that described above, and a 3-hydroxy-camphor which is distinct from that obtained chemically (*Reinartz* and *Zanke*, Ber. **67**, 549). The mixture of 3-hydroxy-camphor and 2-hydroxy-epicamphor obtained by the reduction of camphor quinone with Zn dust and acids is of value for the treatment of circulatory and respiratory diseases; it is used in medicine as a 50% alcoholic solution, which is stable, under the name "*oxaphor*".

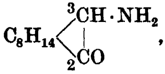
After camphor has been fed to dogs, their urine contains a compound of glucuronic acid (I, 716), which can be decomposed into *camphorol*, $C_{10}H_{16}O_2$, and glucuronic acid. This camphorol is a mixture of hydroxy-camphors, which has been found to contain 5-hydroxy- and two π-hydroxy-camphors, besides the 3-hydroxy-camphor described above. Hence the biological oxidation attacks the camphor molecule in the ortho- and para- positions to the CO group, and also involves both π-carbon atoms (*Asahina* and *Ishidate*, Ber. **67**, 71). The metabolism of camphor probably gives several other products (*Reinartz*, *Zanke* and *Kurschgen*, Ber. **68**, 310).

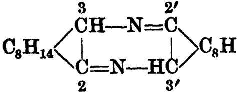
6-Hydroxy-camphor, m.p. (*dl*) 130°, *dinitrobenzoate* m.p. 146°, *semicarbazone* m.p. 200°, is formed from 2:6-diketo-camphane with Zn and HI (*Asahina* and *Tukamoto*, Ber. **70**, 585).

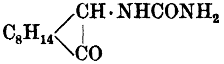
5-Hydroxy-camphor, m.p. 210°, can be obtained by the biological method or by the mild reduction (Na amalgam) of 5-keto-camphor. The *semicarbazone*, m.p. 222°, can be converted into a mixture of epiborneol and epi-isoborneol and hence into epicamphor. The structure of the two π-(8- or 9-)**hydroxy-camphors** (cis, m.p. (active) 234°, *semicarbazone* m.p. 217°; trans, m.p. (active) 233°, *semicarbazone* m.p. 225°) has been established by their relation to *keto-dihydroteresantalic acid* (*cis-π-apocamphor-7-carboxylic acid*), m.p. 270°, and to *iso-ketopinic acid* (*trans-π-apocamphor-7-carboxylic acid*), m.p. 250°, into which they are converted by oxidation. They have been used for the preparation of *π-borneol* and *7-aldehydo-π-apocamphor* in their cis- and trans forms, and for the preparation of the opticals antimers of *π-apocamphane-7-carboxylic acid* (*Asahina* and *Ishidate*, Ber. **67**, 74; Brit. Pat. 441,807 [1935]). The *π-hydroxy-camphor*, m.p. (active cis-) 234°, has also been obtained from π-bromocamphor and from α:π-dihalogeno-camphor; cautious oxidation with CrO_3 converts it into *π-apocamphor-7-aldehyde*, m.p. (active) 204–205° (*Sahashi*, *Takeuchi*, *Shimamoto*, *Iki* and *Takebe*, C. 1935 I 2021; *Kenkyujo*, French Pat. 790,220 [1935]; *Asahina* and *Ishidate*, French Pat. 791,378 [1936]).

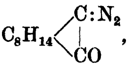
4-Hydroxy-camphor, $C_{10}H_{16}O_2$, m.p. (active) 250°, is formed by the action of nitrous acid upon *4-amino-camphor*, $C_{10}H_{15}O(NH_2)$, m.p. (active) 230–232°, which is obtained from camphor-4-carboxylic acid (*Houben* and *Pfankuch*, Ann. **489**, 217).

10-Hydroxy-camphor, *ω-hydroxy-2-keto-camphane* $C_{10}H_{16}O_2$, m.p. (active) 220° (*semicarbazone* m.p. 200°), is obtained in the *d*-form by the reduction of the semicarbazone of the methyl ester of *d*-ketopinic acid, m.p. 216°, with Na and alcohol; it is also formed by hydrolysis of the esters obtained from 10-bromocamphor and organic acids (*Sahashi, Takeuchi, Shimamoto, Iki* and *Takebe*, C. 1935 I 2021; *Kenkyujo*, French Pat. 790,220 [1935]; *Asahina* and *Ishidate*, French Pat. 791,378 [1935]). Oxidation with bichromate and sulphuric acid gives the *aldehyde of ketopinic acid, ω:2-diketo-camphane*, m.p. 210–213°. Decomposition of the semicarbazone of 10-hydroxy-camphor with sodium ethoxide yields *10-hydroxy-camphane, apocamphane-1-carbinol* (*ω-borneol*), m.p. 200–201°; oxidation of this gives *10-keto-camphane, ω-camphor, apocamphane-1-aldehyde*, m.p. 187–189° (*Asahina* and *Ishidate*, Ber. **67**, 1202).

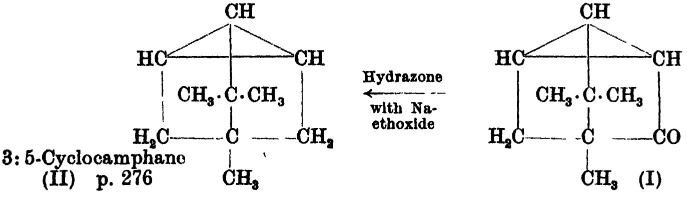
Amino-derivatives of Camphor. — 3-Amino-camphor  $C_8H_{14}\left<\begin{matrix}{}^3CH\cdot NH_2\\ |\\ {}_2CO\end{matrix}\right.$, b.p. 244°, is obtained from nitrocamphor, or, better, from isonitroso-camphor, by reduction. It is an unstable, waxy mass with a fishy smell; it condenses with itself merely on standing to give *dihydro-dicamphene-pyrazine*,



, m.p. 116°; as an α-aminoketone it forms heterocyclic rings very readily (cf. *Duden* and *Treff*, Ann. **313**, 25). *Amino-camphor hydrochloride*, m.p. 224°, has a similar physiological effect to curare, but is much weaker. *Acetyl compound*, m.p. 122°. *Camphoryl-glycine ester*, $(C_{10}H_{15}O)NHCH_2CO_2Et$, is poisonous (*Duden*, Ann. **307**, 207; *Manasse*, Ber. **31**, 3260; *Duden* and *Pritzkow*, Ber. **32**, 1538; *Einhorn* and *Jahn*, Ber. **35**, 3657). *Camphoryl carbamide*  $C_8H_{14}\left<\begin{matrix}CH\cdot NHCONH_2\\ |\\ CO\end{matrix}\right.$ m.p. 169°, prepared from amino-camphor and potassium cyanate, gives with nitrous acid *camphoryl isocyanate* $(C_{10}H_{15}O)N{:}C{:}O$, m.p. 77°, a very reactive substance from which numerous derivatives of camphor can be obtained. *Camphoryl isothiocyanate*, $(C_{10}H_{15}O)N{:}C{:}S$, has m.p. 106·5° (*Forster* and *Jackson*, J. **91**, 1890). For aryl derivatives of 3-amino-camphor, see *Forster* and *Spinner*, J. **115**, 889; *B. Singh, D. Singh, Dutt* and *G. Singh*, J. **117**, 980. For **4-amino-camphor,** see above.

Diazocamphor, *2-keto-3-diazocamphane,*  $C_8H_{14}\left<\begin{matrix}C{:}N_2\\ |\\ CO\end{matrix}\right.$, yellow crystals of m.p. 75°, is obtained by the action of nitrous acid on amino-camphor hydrochloride (*Angeli*, Ber. **26**, 1718); a better yield is obtained by the oxidation of either of the stereoisomeric camphor quinone 3-monohydrazones with yellow HgO (*Bredt* and *Holz*, J. pr. **95**, 148). With potassium sulphite it gives the salt of a hydrazine-sulphonic acid, which is hydrolysed by conc. HCl into hydrazine and camphor quinone (*Rimini*, Gazz. **26**, II, 290). Diazocamphor is used for the preparation of

3:5- (or *β*-) **Cyclocamphanone,** *epicyclenone* (I)

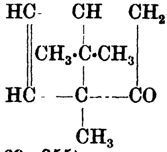


3:5-Cyclocamphane (II) p. 276

(I)

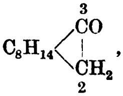
m.p. 166–168°, b.p. 205–207°, which is formed almost quantitatively by heating diazocamphor with copper bronze; *semicarbazone* m.p. 244°; the *hydrazone* m.p. 45°, liquefies on exposure to the air. **3:5-Cyclocamphanol** has m.p. 174–176°, b.p. 205–208°, *phenylurethane* m.p. 106–108°. The proof of the formula of 3:5-cyclocamphanone is given by its degradation to cyclo-isocamphoronic acid (*Bredt* and *Holz*, J. pr. **95**, 133), which is carried out in the same way as the degradation of camphor to isocamphoronic acid (p. 315). Biological oxidation in the animal organism attacks cyclocamphanone in the π-position (*Reinartz*, *Zanke* and *Faust*, Ber. **67**, 1536; *Reinartz*, *Zanke* and *Kürschgen*, Ber. **68**, 310; see p. 291).

6-Keto-bornylene $C_{10}H_{14}O$,

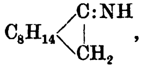


has m.p. 148° (*Asahina*, *Ishidate* and *Tukamoto*, Ber. **69**, 355).

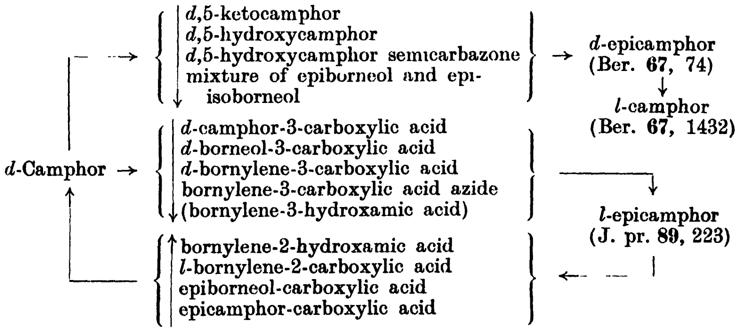
Epicamphor, *β-camphor, 3-keto-camphane*


$C_8H_{14}\left\langle\begin{array}{l}\overset{3}{CO}\\ |\\ \underset{2}{CH_2}\end{array}\right.$

, m.p. (active) 184°, (*dl*) 180°, b.p. 212·5°/747·5 mm., $[\alpha]_D^{19} \pm 58{\cdot}4°$ (in benzene). The *l*-form corresponds to *d*-camphor, and the *d*-form to *l*-camphor. It is prepared by hydrolysing epicamphor-imine,

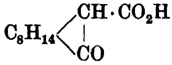
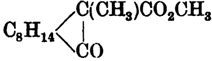
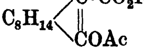
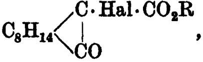

$C_8H_{14}\left\langle\begin{array}{l}C{:}NH\\ |\\ CH_2\end{array}\right.$

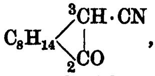
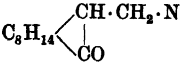
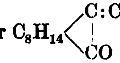
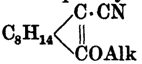
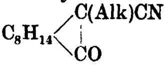
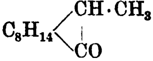
, with acids; the latter compound can be obtained from the azide of bornylene-carboxylic acid (p. 296) by the Curtius reaction. In a similar way, bornylene-hydroxamic acid is converted via the imine into epicamphor (*Bredt* and *Perkin, jun.*, J. pr. **89**, 214; *Bredt-Savelsberg* and *Bund*, J. pr. **131**, 46). Epicamphor (or epiborneol) can be obtained more readily, but in smaller yield, by the oxidation of pinene hydrochloride with chromic acid to 5-keto-2-chlor-camphane, followed by replacement of the Cl by H (*Bredt* and *Pinten*, J. pr. **115**, 54); or directly from camphane by oxidation with CrO_3 (*loc. cit.*, p. 48). For epicamphor from 2-hydroxy-3-ketocamphane, see p. 291; from 5-ketocamphor, see *Asahina* and *Ishidate*, Ber. **66**, 1913. The following table shows the relationships of *d*- and *l*-epicamphor to *d*-camphor:

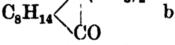

d,5-ketocamphor
d,5-hydroxycamphor
d,5-hydroxycamphor semicarbazone
mixture of epiborneol and epi-isoborneol
d-epicamphor (Ber. **67**, 74)
l-camphor (Ber. **67**, 1432)
d-Camphor
d-camphor-3-carboxylic acid
d-borneol-3-carboxylic acid
d-bornylene-3-carboxylic acid
bornylene-3-carboxylic acid azide
(bornylene-3-hydroxamic acid)
l-epicamphor (J. pr. **89**, 223)
bornylene-2-hydroxamic acid
l-bornylene-2-carboxylic acid
epiborneol-carboxylic acid
epicamphor-carboxylic acid

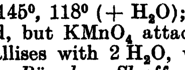
Oxime m.p. (active) 103–104°, (*dl*) 98–100°; *semicarbazone* m.p. (active) 237–238°. *Isonitroso-epicamphor* is prepared in the same way as isonitroso-camphor, and like the latter it exists in two forms, m.p. (active) 170° and 140°; heating converts the second into the first. Both give camphor quinone on warming with conc. HCl, and camphoric acid imide if treated for a short time with conc. sulphuric acid. Reduction leads to *amino-epicamphor*, m.p. (active) 168–170°. Epicamphor is best distinguished from camphor by its bromination product, *2-brom-3-ketocamphane*, m.p. (active) 133–134°, (*dl*) 135°. (*Bredt*, J. pr. **131**, 135). para-*Hydroxy-epicamphor*, *2-hydroxy-5-ketocamphane*, m.p. (active) 240°, (*dl*) 236°, is formed by the hydrolysis of para-*acetoxy-epicamphor*, *p-keto-bornyl acetate*, m.p. (active) 67–77°, (*dl*) 73–75°, the oxidation product of bornyl acetate with chromic acid in acetic acid (*Bredt* and *Goeb*, J. pr. **101**, 285; *Bredt* and *Pinten*, *ib.* **119**, 106). para-*Chlor-epicamphor*, m.p. 158°, is formed in a similar way by the oxidation of bornyl chloride (*Bredt* and *Pinten*, *ib.* **115**, 48); the reduction of p-chlor-epicamphor with Na and alcohol gives epiborneol (p. 279). p-*Brom-epicamphor* (active) m.p. 135° (*Murayama* and *Tanaka*, J. pharm. Soc. Japan **1927**, 131) and *2-brom-6-chlor-epicamphor* (active) m.p. 184° (*Bredt* and *Pinten*, J. pr. **119**, 107). For the biological oxidation of epicamphor to its hydroxy-derivatives (2-hydroxy- and 4-hydroxy-), by feeding to dogs, see *Reinartz* and *Zanke*, Ber. **67**, 589.

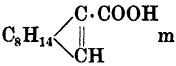
Sodium camphor, $C_{10}H_{15}ONa$, from camphor and sodium or sodamide, and *camphor magnesium bromide*, $(C_{10}H_{15}O)MgBr$, from 3-bromocamphor and Mg in ether, benzene, toluene, etc., are particularly useful for the **introduction of carbon radicals into the camphor molecule.** By the action of alkyl halides (*Haller* and *Bauer*, Ann. chim. (9) **8**, 117; *Haller* and *Louvrier*, *ib.* (9) **9**, 189; French Pat. 736,428 [1932]), CO_2, cyanogen, carboxylic esters, acid chlorides or anhydrides, and aldehydes and ketones on these substances, the following groups can be introduced in place of the H of the $\cdot CH_2\cdot CO\cdot$ group: $\cdot CH_3$, $\cdot CO_2H$, $\cdot CN$, $\cdot COR$, $\cdot CH(OH)R$, $\cdot C(OH)RR'$, $:CHR$; the resulting products are capable of numerous reactions.

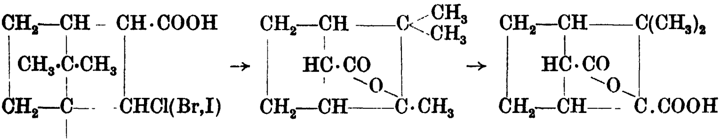
Camphorcarboxylic acid, *camphor-3-carboxylic acid*  $C_8H_{14}\left\langle\begin{array}{l}CH\cdot CO_2H\\ |\\ CO\end{array}\right.$, m.p. (active) 128°, (*dl*) 124° (*Bredt*, J. pr. **131**, 132), with evolution of CO_2, is formed from camphor with sodium, or, better, sodamide, and CO_2 in benzene, or from bromocamphor, Mg and CO_2 in ether (*Brühl*, Ber. **36**, 668, 1305; *Furness* and *Perkin jun.*, J. **105**, 2024). *Methyl ester*, b.p. 155–160°/15 mm.; *ethyl ester* (synthesis: *Ruzicka* and *Kuhn*, Helv. **8**, 752) b.p. 167°/21 mm. The acid and its esters give green and blue colours with ferric chloride (enol reaction). The esters can be alkylated with sodium and alkyl iodide or with dimethyl sulphate, giving esters of alkyl-camphorcarboxylic acids: **methyl-camphorcarboxylic methyl ester**  $C_8H_{14}\left\langle\begin{array}{l}C(CH_3)CO_2CH_3\\ |\\ CO\end{array}\right.$, m.p. 87° (*azide*: m.p. 104° decomp.); **ethyl-camphorcarboxylic ethyl ester,** b.p. 165°/15 mm. These esters are somewhat difficult to hydrolyse; from the latter and anhydrous ethylamine at 150° in a sealed tube **ethyl-camphor** (p. 295) and **ethyl-camphor ethyl-imine** are obtained: the latter gives an aurichloride, $C_{14}H_{25}N\cdot HCl\cdot AuCl_3$, of m.p. 180–182° (*J. Bredt*, private communication). With acyl halides the sodio-derivatives of the camphorcarboxylic esters give O-acylated derivatives:  $C_8H_{14}\left\langle\begin{array}{l}C\cdot CO_2R\\ \|\\ COAc\end{array}\right.$; but with benzene-sulphonic chloride α-chlorocamphorcarboxylic esters and benzene-sulphinic acid are formed. α-Bromocamphorcarboxylic esters and α-iodocamphorcarboxylic esters,  $C_8H_{14}\left\langle\begin{array}{l}C\cdot Hal\cdot CO_2R\\ |\\ CO\end{array}\right.$, are also easy to obtain (*Brühl*, Ber., **36**, 1722). "*Bismocymol*" is the basic Bi salt of camphorcarboxylic acid (*Kolmer*, C. 1931 II 3357).

The nitrile of camphorcarboxylic acid, **3-cyanocamphor,**  $C_8H_{14}\left\langle\begin{array}{l}{}^3CH\cdot CN\\ |\\ {}_2CO\end{array}\right.$, m.p. 127°, is formed from Na-camphor and cyanogen, and, mixed with its oxime, from hydroxymethylene-camphor (p. 298) by warming with hydroxylamine hydrochloride (*Bishop, Claisen* and *Sinclair*, Ann. **281**, 349). The catalytic reduction of 3-cyanocamphor yields **methylene-camphor-α-camphomethylamine** $C_{22}H_{33}O_2N$, m.p. 152°, which is converted by HCl into the hydrochloride of **camphomethylamine**  $C_8H_{14}\left\langle\begin{matrix}CH\cdot CH_2\cdot NH_2\\ |\\ CO\end{matrix}\right.$, b.p. 126–128°/11 mm., and into **methylene-camphor**  $C_8H_{14}\left\langle\begin{matrix}C:CH_2\\ |\\ CO\end{matrix}\right.$ (*Rupe* and *Hodel*, Helv. **7**, 1025; see p. 299); methylene-camphor dibromide has m.p. 108–109°. **Di-camphomethyl-amine,** $(C_{10}H_{15}O)CH_2NH\cdot CH_2(C_{10}H_{15}O)$, m.p. 124°, is formed by the action of NH_3 upon methylene-camphor. The Na-derivative of cyanocamphor yields with alkyl iodides both O- and C-**alkyl-cyanocamphors,**  $C_8H_{14}\left\langle\begin{matrix}C\cdot CN\\ \|\\ COAlk\end{matrix}\right.$ and  $C_8H_{14}\left\langle\begin{matrix}C(Alk)CN\\ |\\ CO\end{matrix}\right.$ (*Haller*, C. r. **136**, 788); hydrolysis of the latter, followed by decarboxylation, gives alkyl-camphors. **3-Methyl-camphor,**  $C_8H_{14}\left\langle\begin{matrix}CH\cdot CH_3\\ |\\ CO\end{matrix}\right.$ m.p. (active) 38° (see also *Rupe* and *Lenzlinger*, Helv. **18**, 255), can be prepared in this way, and is also obtained by the hydrolysis of methyl-camphorcarboxylic ester with alcoholic potash under pressure. Na-camphor and CH_3I give a mixture of 3-methyl- and 3:3-dimethylcamphor, and the former can be separated as its oxime from the dimethyl compound by means of hydroxylamine-zinc chloride. **Ethyl-camphor** has b.p. 108°/14 mm.; **ethylidene-camphor,** $(C_{10}H_{14}O):CHCH_3$, has b.p. 110–115°/10 mm., $[\alpha]_D + 113°$ (*Minguin*, C. r. **138**, 577); **diethyl-camphor** has b.p. 133°/14 mm.; for other homologues, see *Haller* and *Louvrier*, C. r. **158**, 754; *Haller* and *Bauer*, Ann. chim. (9) **8**, 117. **3-Hydroxy-3-cyano-camphor** is formed by the addition of HCN to camphor quinone; fuming sulphuric acid hydrolyses it to the *amide*, $C_{10}H_{14}O(OH)(CONH_2)$, m.p. 235–240°, and further hydrolysis yields *3-hydroxy-camphor-carboxylic acid* in two stereoisomeric forms of m.p. 207–208° and 184° (decomp.). Its decomposition leads to a mixture of 2-hydroxy-epicamphor and 3-hydroxy-camphor, which is probably due to the intermediate formation of dihydroxy-bornylene (p. 290). The *acetate* of 3-hydroxy-camphorcarboxylic acid, m.p. 90–91°, on the other hand, gives on decomposition only 3-hydroxy-camphor in the form of its acetate (*Bredt*, J. pr. **131**, 49).

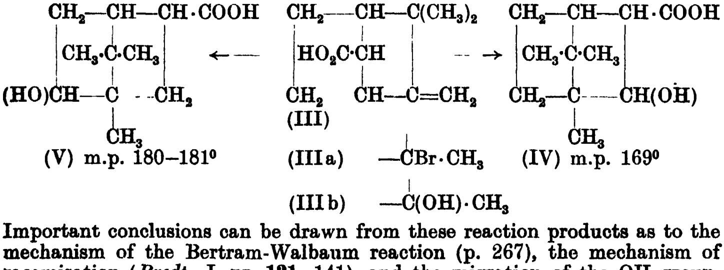
3:3-Dimethyl-camphor  $C_8H_{14}\left\langle\begin{matrix}C(CH_3)_2\\ |\\ CO\end{matrix}\right.$ b.p. 106°/11 mm., from Na-camphor and CH_3I, is a mobile liquid, smelling of both camphor and menthone; it forms neither oxime nor semicarbazone; when warmed with $NaNH_2$ the ring is opened to give the amide of dimethyl-campholic acid (p. 304) (cf. the analogous reaction with camphenilone and fenchone) (*Haller* and *Bauer*, C. r. **148**, 1643).

The electrolytic reduction of camphor-3-carboxylic acid at an amalgamated cathode (*Bredt*, J. pr. **104**, 1) yields cis- and **trans-borneol-3-carboxylic acids,**  $C_8H_{14}\left\langle\begin{matrix}CH\cdot COOH\\ |\\ CHOH\end{matrix}\right.$ m.ps. (active) 101°, (*dl*) 130°, and (active) 171°, (*dl*) 145°, 118° (+ H_2O); both acids are oxidised to camphoric acid by nitric acid, but $KMnO_4$ attacks only the cis-acid. The Ca salt of the cis-acid crystallises with 2 H_2O, while the Ca salt of the trans-acid is anhydrous (see also *Böeseken, Slooff* and *Lutgerhorst*, C. 1932 I 1782). Both acids with acetyl chloride give the *acetate* of the trans-acid, m.p. (active) 123°, (*dl*) 124°. The cis-acid loses water much more easily than the trans-acid, but with acetyl chloride or acetic anhydride both give

Bornylene-3-carboxylic acid, 
$C_8H_{14}\langle C\cdot COOH \,\|\, CH$ m.p. (active) 113°, (*dl*) 109°, b.p. 158°/13 mm. (*Bredt*, J. pr. **131**, 132); oxidation of this with $KMnO_4$ gives *2-hydroxy-2:3-oxido-camphane-3-carboxylic acid*, $C_{11}H_{16}O_4$, m.p. 208°, and then camphoric acid (*Bredt*, J. pr. **131**, 63). The *hydrochloride*, m.p. 202°, of the *hydrazide* of *bornylene-carboxylic acid*, m.p. 109–110°, can be converted into the azide with sodium nitrite, and this can give the urethane and then epicamphor. Epicamphor can also be prepared from bornylene-hydroxamic acid (*Bredt* and *Perkin jun.*, J. pr. **89**, 225). The simplest method of passing from bornylene-carboxylic acid to epicamphor is via the *acid chloride*, b.p. 120–121°/19 mm., which with sodium azide gives the acid azide; the latter is converted by HCl into epicamphorimine hydrochloride, and this with water yields epicamphor (*Bredt-Savelsberg* and *Bund*, J. pr. **131**, 46). Bornylene-carboxylic acid combines with HCl, HBr and HI in acetic acid to give *β-chloro-*, *β-bromo-* and *β-iodo-hydrobornylene-carboxylic acids* (*2-chloro-*, *2-bromo-* and *2-iodo-camphane-3-carboxylic acids*) (I), m.ps. 85°, 91° and 130° (*Bredt* and *Hilbing*, J. pr. **84**, 782); the alkali salts of these acids are sparingly soluble in water, and when boiled in aqueous solution, yield: (1) bornylene; (2) bornylene-3-carboxylic acid; (3) **camphene hydrate mesocarboxylic acid lactone** (II), m.p. 183°, which is oxidised by nitric acid to **mesocarboxy-camphenilolic acid lactone** (IIa), m.p. 230° (*Bredt*, J. pr. **104**, 27):

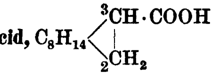

(I) (II) (IIa)

A similar rearrangement has thus taken place as in the conversion of bornyl chloride into camphene. If in the addition of hydrogen halide to bornylene-carboxylic acid a different solvent is used, the trans-acid corresponding to the lactone (II) can be obtained; HBr then yields **camphene-hydrobromide-trans-mesocarboxylic acid** (IIIa), m.p. 157°, which can be separated from the 2-bromocamphane-3-carboxylic acid also formed because of its low solubility in ligroin. Treatment of the acid (IIIa) with alkali replaces the Br by OH, to give **camphene-hydrate-trans-mesocarboxylic acid** (IIIb), m.p. 176°, which by dehydration yields **camphene-trans-meso-carboxylic acid** (III), m.p. 76–77°. This acid is converted back into the hydrobromide (IIIa) again by fuming hydrobromic acid, but with sulphuric-acetic acid it undergoes a retrograde rearrangement to the *dl*-**acetate** (m.p. 116°) of **isoborneol-trans-o-carboxylic acid** (IV) and the *dl*-**acetate** (m.p. 159°) of **isoborneol-p-carboxylic acid** (V) (*Bredt*, J. pr. **104**, 7; **131**, 137):

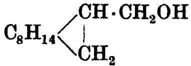


(V) m.p. 180–181° (IV) m.p. 169°

Important conclusions can be drawn from these reaction products as to the mechanism of the Bertram-Walbaum reaction (p. 267), the mechanism of racemisation (*Bredt*, J. pr. 131, 141), and the migration of the OH group, which in the rearrangement of IIIb can move either to the 2-position of the camphane ring, as in IV, or to the 6-position, as in V.

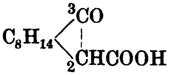


Camphane-3-carboxylic acid, $C_8H_{14}\left\langle\begin{array}{l}{}^{3}CH\cdot COOH\\ \vert\\ {}_{2}CH_2\end{array}\right.$ m.p. 91°, b.p. 153°/13 mm., *amide* m.p. 166–167°, is formed by the reduction of 2-halogeno-camphane-3-carboxylic acids with K-amalgam, or by the catalytic reduction of bornylene-3-carboxylic acid with H_2 and Pd (*Bredt*, Ann. **366**, 60; *Bredt* and *Hilbing*, J. pr. **84**, 785; *Bredt* and *Perkin jun.*, J. pr. **89**, 232; *Rupe*, Ann. **440**, 234).



Camphane-3-carbinol, *3-hydroxymethyl-camphane* $C_8H_{14}\left\langle\begin{array}{l}CH\cdot CH_2OH\\ \vert\\ CH_2\end{array}\right.$, m.p. 28°, b.p. 118°/11 mm., is formed by the reduction of camphane-3-carboxylic ester with Na and alcohol; it is dehydrated by phosphoric acid to **3-methylene-camphane,** b.p. 58–62°/11 mm. (*Rupe* and *Brin*, Helv. **7**, 546; *Rupe*, Ann. **440**, 241; *Rupe* and *Lenzlinger*, Helv. **18**, 255).

For **bornylene-3-methyl ketone** and **camphyl-3-methyl ketone,** see *Rupe* and *Kopp*, Ann. **440**, 215, 227.



Epicamphor-2-carboxylic acid, $C_8H_{14}\left\langle\begin{array}{l}{}^{3}CO\\ \vert\\ {}_{2}CHCOOH\end{array}\right.$ m.p. 120–122°, and some of its derivatives and reaction products have been made by methods similar to those for camphor-3-carboxylic acid: **2-bromoepicamphor-2-carboxylic acid** melts at 145° with decomposition into 2-bromo-epicamphor; **epiborneol-2-carboxylic acid** is known in all four possible stereoisomeric forms, m.ps. 125°, 145°, 173°, 237°; **bornylene-2-carboxylic acid,** m.p. 115°, can be converted into camphor by the methods described under epicamphor (*Bredt* and *Perkin jun.*, J. pr. **89**, 243) (p. 293). **Camphane-2-carboxylic acid,** $C_{11}H_{18}O_2$, m.p. 78–80°, b.p. 155°/15 mm., can be obtained from bornylene-2-carboxylic acid by reduction with H_2 and Pd (*id. ib.* 250).

Like bornyl acetate and bornyl chloride, camphane-2-carboxylic ester can be oxidised to a 5-keto-derivative, **epicamphor-p-carboxylic acid,** *5-keto-camphane-2-carboxylic acid* $C_{11}H_{16}O_3$, m.p. 185° (*Murayama* and *Tanaka*, J. pharm. Soc. Japan **1926**, No. 527, 1). The lower homologue of camphane-2-carboxylic acid, **apocamphane-2-carboxylic acid,** $C_{10}H_{16}O_2$, m.p. 105°, is a product of the ozonisation of α-fenchene (*Komppa* and *Roschier*, C. 1917 I 751; 1918 I 623).

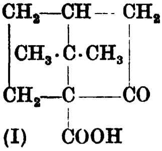
2-Chlorocamphane-2-carboxylic acid, the chlorination product of camphane-2-carboxylic acid, can undergo the camphene rearrangement when HCl is removed, giving **camphene-1-carboxylic acid,** $C_{11}H_{16}O_2$, m.p. 109–110°; this is hydrated in the Bertram-Walbaum reaction, undergoing a Nametkin rearrangement to give the acetate of isoborneol-4-carboxylic acid (as formulated on p. 300, $\cdot CO_2H$ instead of $\cdot Cl$), which after hydrolysis can be oxidised to **camphor-4-carboxylic acid,** *2-keto-camphane-4-carboxylic acid,* $C_{11}H_{16}O_3$, m.p. 238–240°. From the latter, 4-amino- and 4-hydroxycamphor can be prepared (*Houben* and *Pfankuch*, Ann. **489**, 216) (see also p. 291).

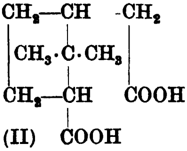
In addition to these camphor-carboxylic acids, two ketonic acids with one C-atom less will be mentioned, apocamphor-1-carboxylic acid or ketopinic acid, and camphenilone-1-carboxylic acid or camphenonic acid.

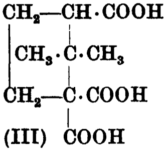
Ketopinic acid, *2-keto-apocamphane-1-carboxylic acid* (I), $C_{10}H_{14}O_3$, m.p. 234°, is formed by the oxidation of bornyl chloride with fuming nitric acid (*Gilles* and *Renwick*, Proc. **1896/97**, 158; *Wedekind*, Z. angew. Chem. **38**, 316), by the oxidation of 2-hydroxy-ω:ω-dinitrocamphane $C_9H_{14}(OH)\cdot CH(NO_2)_2$, with $KMnO_4$ (*Lipp*, Ann. **899**, 257), and from tricyclenic acid according to the scheme:

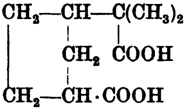
$$\begin{tikzcd}
\begin{array}{c}C_{10}H_{14}O_2\\ \text{Tricyclenic acid}\end{array} \arrow[r, dashed, "+HBr"] & \begin{array}{c}C_{10}H_{15}O_2Br\ (\text{m.p. }197^\circ)\\ \text{Bromapocamphane-carboxylic acid}\end{array} \arrow[d, "NaOH"] \\
\begin{array}{c}C_{10}H_{14}O_3\\ \text{Ketopinic acid}\end{array} & \begin{array}{c}C_{10}H_{16}O_3\ (\text{m.p. }237^\circ)\\ \text{Hydroxy-apocamphane-carboxylic acid}\end{array} \arrow[l, dashed, "O_2"']
\end{tikzcd}$$

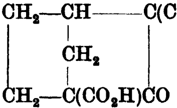
With sodium methoxide the ring system of ketopinic acid (I) opens to give **pinophanic acid** (II), m.p. 203° (cf. the opening of camphor to campholic acid), while oxidation with nitric acid yields *carboxy-apocamphoric acid* (III) (*Bredt*, C. 1927 II 2298; *Bredt* and *May*, Ch. Ztg. **34**, 65). Although they are β-ketonic acids, both ketopinic and camphenonic (see below) acids are stable to heat (*Bredt*, C. 1927 II 2298). If the CO_2 is removed by vigorous treatment, the bicyclic system is destroyed by fission at the bridge and a cyclohexenone derivative is obtained (*Wedekind*, Z. angew. Chem. **38**, 316):


(I)


(II)

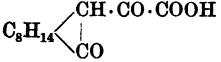
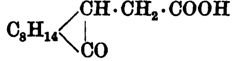
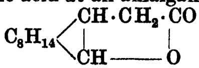

(III)

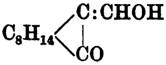

(IV)

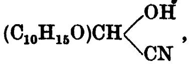
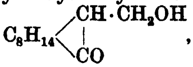
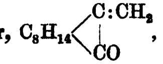
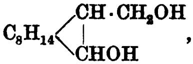
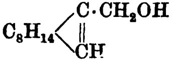

(V)

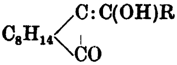
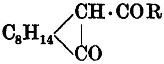
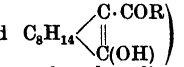
Isoketopinic acid and **keto-dihydro-teresantalic acid** are carboxylic acids of the π-apocamphor series (see *Hasselström*, C. 1931 II 1412, and p. 291).

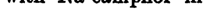
Camphenonic acid (V), $C_{10}H_{14}O_3$, m.p. (*dl*) 134°, (active) 70° ($+ 1H_2O$), 106° (anhydrous), is formed from camphenic acid (IV) by heating with acetic anhydride (see also *Aschan*, C. 1935 II 1555). *Amide*, m.p. (*dl*) 185°, (active) 152–154°. Camphenonic acid is stable towards oxidising agents; when heated with sodium ethoxide under pressure it reverts to camphenic acid (cf. formation of pinophanic acid from ketopinic acid) (*Aschan*, Ann. **410**, 240; cf. *Houben* and *Willfroth*, Ber. **46**, 2283, 2298). Reduction of camphenonic acid with Na and alcohol gives **camphenolic acid,** $C_{14}H_{16}O_3$, m.p. (*dl*) 99–100°, which has a charateristic sodium salt, difficultly soluble in alkali. Camphenonic acid can be converted into fenchone by reducing the COOH group to CH_3 (*Komppa* and *Klami*, Ber. **68**, 2001).

Na-Camphor condenses with oxalic ester to give the ester of **camphor-oxalic acid,** *camphoryl-glyoxylic acid*  $C_8H_{14}\left\langle\begin{matrix}CH\cdot CO\cdot COOH\\ |\\ CO\end{matrix}\right.$, m.p. 88° (*B. Tingle* and *A. Tingle*, Am. **23**, 214; *B. Tingle*, *ib.* 363; *Tingle* and *Williams*, *ib.* **39**, 277). This is reduced by amalgamated Zn and HCl to *camphoryl acetic acid*  $C_8H_{14}\left\langle\begin{matrix}CH\cdot CH_2\cdot COOH\\ |\\ CO\end{matrix}\right.$ m.p. (active) 83°, (*dl*) 112°, which can also be prepared from **camphormethylene-carboxylic acid,** *camphorylidene-acetic acid* $(C_{10}H_{14}O){:}CH\cdot COOH$, by reduction with Na amalgam (*Haller* and *Palfray*, C. r. **176**, 1193; see p. 299). The electrolytic reduction of camphoryl-acetic acid at an amalgamated electrode yields the **lactone** of **borneol-acetic acid,**  $C_8H_{14}\left\langle\begin{matrix}CH\cdot CH_2\cdot CO\\ |\qquad\quad |\\ CH\text{——}O\end{matrix}\right.$ m.p. 58°, b.p. 132°/3 mm. (*J. Bredt*, private communication).

Hydroxymethylene-camphor, *formyl-camphor*  $C_8H_{14}\left\langle\begin{matrix}C{:}CHOH\\ |\\ CO\end{matrix}\right.$ m.p. 80°, b.p. 138°/28 mm., is obtained from Na-camphor or camphor -Mg-bromide and formic ester, and by the action of alcohol-free sodium methoxide upon 3-monohalogeno- and dihalogeno-camphors (*Brühl*, Ber. **37**, 2069; *Rupe*, *Henke* and *Bürki*, Helv. **19**, 698). It behaves as a strong acid. *Methyl ether*

$(C_{10}H_{14}O){:}CHOCH_3$, m.p. 40°, b.p. 202°; *acetate* $(C_{10}H_{14}O){:}CHOCOCH_3$, m.p. 63°, b.p. 200–203°. PCl_3 gives *chlormethylene-camphor* $(C_{10}H_{14}O){:}CHCl$, b.p. 119°/16 mm.; bromine or iodine in neutral solution yield *bromo-* or *iodo-formyl-camphor*, m.ps. 41° and 68°. The *cyanohydrin*  $(C_{10}H_{15}O)CH\left\langle\begin{array}{l}OH\\CN\end{array}\right.$, m.p. 122°, is formed by the action of HCN, and when this is boiled with acetic anhydride it gives *cyanomethylene-camphor* $(C_{10}H_{14}O){:}CHCN$, m.p. 46°, b.p. 280°, the *nitrile of camphorylidene-acetic acid* $(C_{10}H_{14}O){:}CH\cdot COOH$, m.p. 101° (*Claisen*, Ann. **281**, 306). Reduction of hydroxymethylene-camphor with Ni and H_2 gives **camphoryl-carbinol,**  $C_8H_{14}\left\langle\begin{array}{l}CH\cdot CH_2OH\\|\\CO\end{array}\right.$, b.p. 140°/9 mm., *benzoate*, m.p. (active) 97° (*Rupe*, *Ackermann* and *Takagi*, Helv. 1, 452), which can be converted via *camphoryl-methyl bromide*, m.p. 66°, into **methylene-camphor,**  $C_8H_{14}\left\langle\begin{array}{l}C{:}CH_2\\|\\CO\end{array}\right.$, m.p. (active) 44°, b.p. 85°/9 mm. (p. 295). Two stereoisomeric **camphyl-glycols,**  $C_8H_{14}\left\langle\begin{array}{l}CH\cdot CH_2OH\\|\\CHOH\end{array}\right.$, m.p. (cis-) 87°, (trans-) 118°, are formed by the reduction of formyl-camphor with Na and alcohol. $KMnO_4$ oxidises the trans-glycol to trans-borneol-carboxylic acid (p. 295), but the cis-glycol gives camphoric acid, probably with the intermediate formation of cis-borneol-carboxylic acid, which is unstable to permanganate (*Bredt* and *Sandkuhl*, Ann. **366**, 62). The trans-glycol is stable when boiled with HCl in benzene solution, but the cis-glycol under these conditions gives **bornylene-carbinol,**  $C_8H_{14}\left\langle\begin{array}{l}C\cdot CH_2OH\\\|\\CH\end{array}\right.$ m.p. 68° (*id. ib.*). For **hydroxymethylene-epicamphor,** m.p. 89°, see *Perkin jun.* and *Titley*, J. **119**, 1089.

The homologous **acyl-camphors,**  $C_8H_{14}\left\langle\begin{array}{l}C{:}C(OH)R\\|\\CO\end{array}\right.$ (tautomeric forms:  $C_8H_{14}\left\langle\begin{array}{l}CH\cdot COR\\|\\CO\end{array}\right.$ and  $C_8H_{14}\left\langle\begin{array}{l}C\cdot COR\\\|\\C(OH)\end{array}\right.$) are obtained from camphor Mg bromide by the action of carboxylic esters, chlorides or anhydrides, di-camphoryl-alkyl carbinols, $(C_{10}H_{15}O)_2C(OH)Alk$, being by-products (*Malmgren*, Ber. **36**, 2633; *Brühl*, *ib.* **37**, 762), and by the action of alkyl Mg halides upon cyano-camphor (*Forster* and *Judd*, Proc. **21**, 116). **Acetyl-, propionyl-, butyryl-** and **isovaleryl-camphor** have b.ps. 118°/11, 129°/11, 132°/11 and 141–148°/11 mm. **Benzoyl-camphor** exists in two forms, m.p. 87–88° and 89°, and can also be obtained by the action of benzoyl chloride upon Na-camphor in toluene (*Forster*, J. **83**, 98; *Lowry*, J. **123**, 2022; **1928**, 1333).

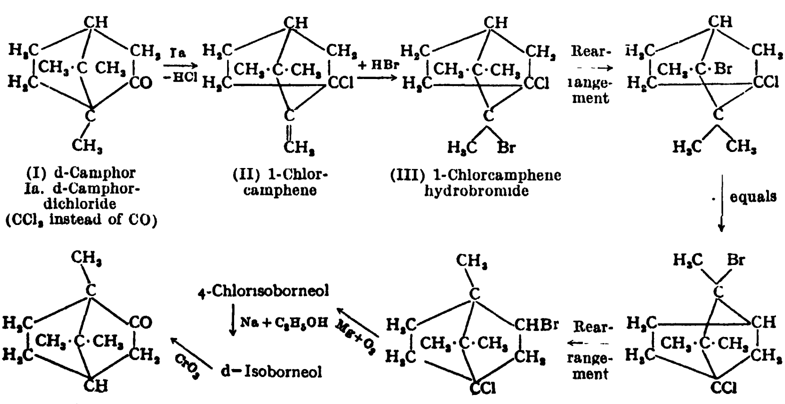
By the condensation of camphor magnesium bromide with aldehydes and ketones in ether, secondary and tertiary alcohols are obtained, some of which can be readily dehydrated. **Camphoryl-methyl-carbinol,** $(C_{10}H_{15}O)CH(OH)CH_3$, b.p. 223–226°, is prepared in small yield, together with acetyl-camphor (see above), by the action of camphor-Mg-bromide upon acetaldehyde; benzaldehyde and camphor-Mg-bromide give exclusively benzoyl-camphor. Na-camphor and benzaldehyde, however, yield **benzylidene-camphor,** $(C_{10}H_{14}O){:}CHC_6H_5$, m.p. 96°, which is also formed by the reduction of benzoyl-camphor; further reduction gives **benzyl-camphor** $(C_{10}H_{15}O)CH_2C_6H_5$, m.p. 128°, while heating with HBr opens the ring to form benzylidene-campholic acid,  $C_8H_{14}\left\langle\begin{array}{l}CH{:}CHC_6H_5\\COOH\end{array}\right.$ (see p. 303). Other aromatic aldehydes condense with Na-camphor in a similar way (*Haller* and *Minguin*, C. r. **133**, 79).

$(C_{10}H_{15}O)MgBr$ reacts with acetone to form **camphoryl-dimethyl-carbinol** $(C_{10}H_{15}O)CMe_2(OH)$, m.p. 88°, b.p. 210–215°, which is converted into **isopropylidene-camphor**, $(C_{10}H_{15}O){:}C(CH_3)_2$, b.p. 200–204°, by boiling with dilute sulphuric acid. **Camphoryl-diphenyl-carbinol**, $(C_{10}H_{15}O)\cdot C(OH)(C_6H_5)_2$, m.p. 122°, is formed from camphor Mg bromide and benzophenone (*Malmgren*, Ber. **36**, 2627).

While on the one hand, as has been shown above, the 3-substitution products of camphor are readily accessible, the preparation of the 4-substituted products is not so simple and molecular rearrangements must be used. These, however, follow a general rule, which is illustrated in the preparation of 4-methyl-camphor: the dehydration of tertiary methyl-borneol, obtained from camphor and CH_3MgI (or from tertiary methyl-fenchol), gives chiefly 1-methylcamphene, corresponding to the formation of camphene from isoborneol; treatment of 1-methyl-camphene with acetic-sulphuric acids gives 4-methylcamphene and then *dl*-4-methyl-isoborneol (Nametkin's rearrangement, see p. 267), and the oxidation of the latter yields *dl-4-methyl-camphor*, m.p. 168° (*Bredt-Savelsberg* and *Buchkremer*, Ber. **64**, 600). In a similar manner the following compounds have been obtained in the *dl*-form: *4-phenyl-camphor*, m.p. 69° (*ib. id.*, **66**, 1921); *4-chlorocamphor*, m.p. 199° (*Houben* and *Pfankuch*, Ann. **489**, 221); *camphor-4-carboxylic acid*, m.p. 240° (p. 297); see also *4-propyl-camphor*, *Nametkin* and *Shawrigin*, Ber. **66**, 511; Ann. **516**, 199. This series of reactions is possible because of the great mobility of the camphane ring-system; from the point of view of the mechanism it is particularly important to note that *d*-camphor can be converted to *l*-camphor in this way (*Houben* and *Pfankuch*, Ann. **507**, 37), as shown by the formulae given below (cf. also pp. 266 and 267). If Cl in formulae (II) to (V) is replaced by CH_3, C_6H_5, or COOH, and Br in formulae (III) to (V) is replaced by $OCOCH_3$, then the sequence shows the formation of 4-substituted isoborneols, which lead to 4-methyl-, 4-phenyl-camphor and to camphor-4-carboxylic acid (see above). 4-Benzyl-camphor cannot be obtained by this method, since the dehydration of tertiary benzyl-borneol takes place without rearrangement, and gives no 1-benzyl-camphene (*Nametkin* and *Strugatzki*, C. 1937 I 1953).

5- and 6-Alkyl derivatives of camphor have not yet been obtained, but should be readily accessible from p-keto-camphor.

Products of the ring-fission of camphor. — The fission of the camphor ring-system can take place initially in two different ways: (1) the bridge,



(I) d-Camphor
Ia. d-Camphor-dichloride
(CCl_2 instead of CO)

(II) 1-Chlor-camphene

(III) 1-Chlorcamphene hydrobromide

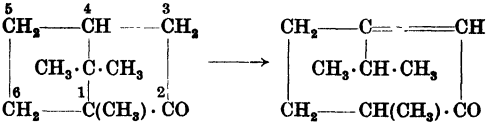
(IV) 4-Chlorcamphene hydrobromide

(V) 4-Chloriso-bornyl bromide

(VI) l-Camphor

which is in a strained configuration (cf. p. 182; *W. Huckel*, Ann. **455**, 123), is broken between C_1 and C_7; (2) the keto-group is attacked and the ring is opened to give derivatives of cyclopentane containing the "*camphoceane*" ring (cf. *Bredt*, Ann. **299**, 162). Examples of the first way are the rearrangements of camphor into cymene, carvacrol and carvenone (p. 234; *Bredt, Rochussen* and *Monheim*, Ann. **314**, 371):

Camphor



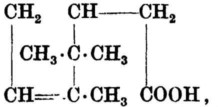
Carvenone.

cf. also the analogous behaviour of carone and α-pinene (pp. 249 and 252).

The second group of reactions of this kind includes the conversion of camphor into α-campholenic acid, campholic acid and camphoric acid. In these reactions the 6-membered ring is opened either (a) between C_1 and C_2 (α-campholenic acid); or (b) between C_2 and C_3 (campholic acid and camphoric acid). In the rearrangement of camphor quinone with fuming sulphuric acid the ring is opened first between C_2 and C_3; ring enlargement then follows, to give trimethyl-cyclohexanone-carboxylic acid (p. 289).

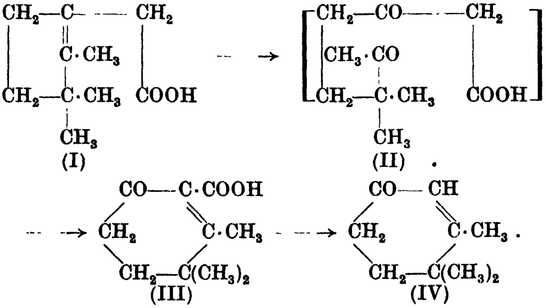
(a) The fission of the camphane ring-system between C_1 and C_2 can be brought about very easily by the action of mineral acids upon camphor oxime; this gives a mixture of α- and β-campholenic nitriles, iso-aminocamphor and dihydrocampholenolactone.

α-Campholenic acid,

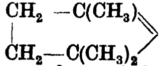


b.p. 256°, 142–142·5°/10·5 mm.; d_0^{15} 1·009, d^{19} 0·992; n_D^{15} 1·4746; optically active. **Campholenic aldehyde,** $C_{10}H_{16}O$, b.p. 83°/12·5 mm., (*semicarbazone* m.p. 138–139°), is formed from pinene oxide and $ZnBr_2$ (*Arbusov*, Ber. **68**, 1430). The *nitrile*, b.p. 226°, of the acid is formed by the dehydration of camphor oxime with dilute sulphuric acid or acetyl chloride; reduction of the nitrile gives *α-camphylamine* $C_{10}H_{17}NH_2$, b.p. 195°; hydrolysis with alcoholic potash yields *α-campholenic amide*, m.p. 130°, which is converted by alkaline hypobromite into the lower homologue of camphylamine, *α-aminocampholene* $C_9H_{15}NH_2$, b.p. 185° (*Blaise* and *Blanc*, C. r. **129**, 106). Further hydrolysis of the amide gives α-campholenic acid. Oxidation of the latter with $KMnO_4$ yields **dihydroxy-dihydro-α-campholenic acid** $C_9H_{15}(OH)_2COOH$, m.p. (active) 144°, (*dl*) 139°, (cf. p. 254), and a ketonic acid, **α-campholonic acid**; this was originally supposed to be pinonic acid, but has now been shown to be *2:3:3-trimethyl-cyclopentanone-4-acetic acid* $C_{10}H_{16}O_3$, b.p. 186°/9 mm.; *oxime* m.p. 188°. α-Campholonic acid is converted on heating into 2:6-diketocamphane, and can be obtained from this compound by the action of dilute HCl upon the di-semicarbazone, which decomposes at 290° (*Komppa* and *Beckmann*, Ber. **69**, 2788; see also p. 289). The oxidation of α-campholenic or of dihydroxy-dihydro-α-campholenic acids with chromic acid gives **iso-ketocamphoric acid,** $C_{10}H_{16}O_5$ or $CH_3{\cdot}CO{\cdot}C(CH_3)_2{\cdot}CH(CH_2COOH)_2$, and then **isocamphoronic acid,** $HOOC{\cdot}C(CH_3)_2CH(CH_2COOH)_2$, m.p. 167° (*Bredt*, Ann. **289**, 19; *Perkin jun.* and *Thorpe*, J. **75**, 897); the latter is converted by heating with sulphuric acid into terpenylic acid (p. 255), CO being evolved (*Tiemann*, Ber. **29**, 3006). For the reduction of α-campholenic acid to α-campholanic acid, see p. 303; for campholenyl ketone, see *Tiffeneau, Lévy* and *Ditz*, Bull. **2** (1935), 1855. α-Campholenic acid is stable towards alkalis, but with acids it rearranges in a peculiar way (*Bredt, Rochussen* and *Monheim*, Ch. Ztg. **24**, 858) into:

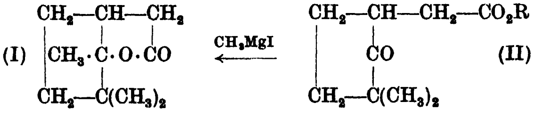
β-Campholenic acid (I), m.p. 52°, b.p. 245°. This acid is optically inactive, since it contains no asymmetric carbon atom. Its *nitrile*, b.p. 225°, is formed by the action of strong acids (strong hydriodic acid) on camphor oxime; on reduction it gives *β-camphylamine*, b.p. 197°, and when it is hydrolysed, the first product is an *amide*, m.p. 86°, which is converted into *β-amino-campholene* with bromine and alkali (*Blaise* and *Blanc*, C. r. **129**, 106). $KMnO_4$ oxidises *β*-campholenic acid to a *dihydroxy-dihydro-acid*, m.p. 146°, and then via a hypothetical intermediate (II) into an oily acid (III), the ring beingt enlarged; (III) readily loses CO_2 to form **isocamphorone** (IV), $C_9H_{14}O$, b.p. 217°:



Chromic acid oxidises *β*-campholenic acid to *γ*-acetylisocaproic acid, $CH_3CO{\cdot}C(CH_3)_2{\cdot}CH_2{\cdot}CH_2{\cdot}COOH$, m.p. 48°, which can be degraded by further oxidation to αα-dimethylglutaric acid and αα-dimethylsuccinic acid. The same degradation products are obtained from isocamphorone (*Tiemann*, Ber. **30**, 242; *Bouveault*, Bull. **19** (1898), 565). *β*-Campholenic acid undergoes a curious rearrangement when heated with bromine, giving 1:3:4-xylyl-acetic acid (*Guerbet* and *Béhal*, C. r. **122**, 1493).

Campholene,  , b.p. 134°, is formed by loss of CO_2 from α- or, better, *β*-campholenic acid by the action of heat, and from campholic acid or its chloride with P_2O_5. It has been synthesised by the action of CH_3MgI upon 2:2:5-trimethylcyclopentanone (p. 56), followed by dehydration of the tetramethyl-cyclopentanol so formed (*Blanc*, C. r. **145**, 681). It is optically inactive, and on oxidation gives *ββ*-dimethyl-laevulinic acid, $CH_3{\cdot}CO{\cdot}C(CH_3)_2{\cdot}CH_2{\cdot}COOH$, and αα-dimethylsuccinic acid. *Campholene dibromide* melts at 97°. Heating with hydriodic acid to 280° converts campholene into hexahydro-pseudo-cumene, a reaction similar to the conversion of *β*-campholenic acid into xylyl-acetic acid (*Tiemann*, Ber. **30**, 594), and of camphoric acid into tetrahydro-isoxylene (p. 95) (*Bredt*, Ber. **26**, 3053).

Dihydro-β-campholenolactone (I), m.p. 30°, b.p. 256°, is the lactone of hydroxy-dihydro-*β*-campholenic acid, m.p. 105°; it is obtained in varying yield in the decomposition of camphor oxime with strong acids, and it is also formed from both campholenic acids and from iso-aminocamphor with acids. It has been prepared synthetically by the action of CH_3MgI upon 2:2-dimethylcyclopentanone-5-acetic ester (II) (*Blanc*, C. r., **146**, 77).

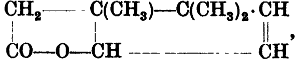


When oxidised with chromic acid, it gives **hydroxy-dihydro-β-campholenolactone,** m.p. 144° (*Tiemann*, Ber. **30**, 411).

Iso-aminocamphor, $C_{10}H_{17}ON$, b.p. 254°, is obtained together with the above substances by the action of strong acids on camphor oxime and the campholenic amides and nitriles; it is also formed from ω-bromocamphor and alcoholic ammonia under pressure (*Forster* and *Howard*, J. **103**, 63).

It is readily converted into dihydro-campholenolactone (*Tiemann*, Ber. **30**, 324), but its structure has not yet been established. The amino-group is probably not in the ω-position, because the unstable hydroxy-compound obtained from it has properties quite different from those of ω-hydroxy-camphor (*Asahina* and *Ishidate*, Ber. **67**, 1203).

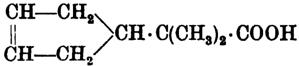
Dihydro-α-campholenic acid, *α-campholanic acid*, $C_{10}H_{18}O_2$, is known in both geometrically isomeric forms; the *nitrile*, b.p. 225–228°, of the trans-*dl*-acid is obtained by heating the isomeric *dl*-camphor-imine (p. 287) in air (*Mahla* and *Tiemann*, Ber. **33**, 1929). Hydrolysis of this nitrile yields trans-*dl*-**dihydro-α-campholenic amide,** m.p. 125°, identical with the hydrogenation product (Pt and H_2) of *dl*-α-campholenic amide (*Lipp*, Ber. **55**, 1883). The cis-form of *dl*-**α-campholanic acid,** b.p. 151°/14 mm., *amide* m.p. 129°, is formed by the catalytic reduction of *dl*-α-campholenic acid (*van Kregten*, Rec. **36**, 64); see also isocampholic acid (p. 304). By bromination and removal of HBr an *isomer* of campholenic acid is obtained, (C_8H_{14}):CH·COOH, m.p. 70°, which is oxidised by $KMnO_4$ to *2:2:3-trimethyl-cyclopentanone*, b.p. 165° (*Blaise* and *Blanc*, Bull. **27** (1902), 71). **β-Campholanic acid** is obtained in a similar manner from β-campholenic acid, and may be degraded via brom-β-campholanic acid and iso-β-Δ^1-campholenic acid, m.p. 95°, to *2:3:3-trimethyl-cyclopentanone* (*van Kregten*, Rec. **36**, 64).

Epicampholenic acid, b.p. 165°/30 mm., is obtained as its *nitrile*, b.p. 147°/100 mm., from epicamphor by a reaction similar to that for α-campholenic acid (*Perkin jun.* and *Titley*, J. **119**, 1089). The *lactone* of *γ-hydroxy-epicampholenic acid* is obtained from the oxime of 5-keto-bornyl acetate (p. 294) by boiling with dilute sulphuric acid: 

$$\begin{array}{llll} CH_2 & —C(CH_3) & —C(CH_3)_2\cdot & CH \\ | & \;\;| & & \| \\ CO—O & —CH & ——— & CH \end{array}$$

, m.p. 69°, b.p. 134–136°/12 mm.; it can be degraded to camphoronic acid (*J. Bredt*, private communication).

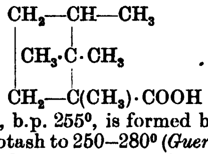
For **cyclo-campholenic acid,** see p. 315; for **fencholenic acids,** see p. 317.

Camphoceenic acid, 

$$\begin{array}{l} CH—CH_2\diagdown \\ \|\qquad\qquad\;\; CH\cdot C(CH_3)_2\cdot COOH \\ CH—CH_2\diagup \end{array}$$

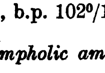
, m.p. 54°, b.p. 145°/14 mm., is obtained from camphenilone oxime, just as campholenic acid is obtained from camphor oxime (*Jagelki*, Ber. **32**, 1505; *Blaise* and *Blanc*, Bull. **23** [1900] 177). Oxidation with $KMnO_4$ gives *dihydroxy-camphoceenic acid*, $C_9H_{16}O_4$, m.p. 163°, and further oxidation with CrO_3 yields gem-dimethyl-tricarballylic acid.

(b) The camphane ring-system is broken between C_2 and C_3 by treatment of camphor with alkali (giving campholic acid), and particularly by the oxidation of 2- or 3-substituted camphane derivatives (giving camphoric acid).

Campholic acid, 

$$\begin{array}{l} CH_2—CH—CH_3 \\ |\qquad\;\; | \\ |\; CH_3\cdot C\cdot CH_3 \\ |\qquad\;\; | \\ CH_2—C(CH_3)\cdot COOH \end{array}$$

.

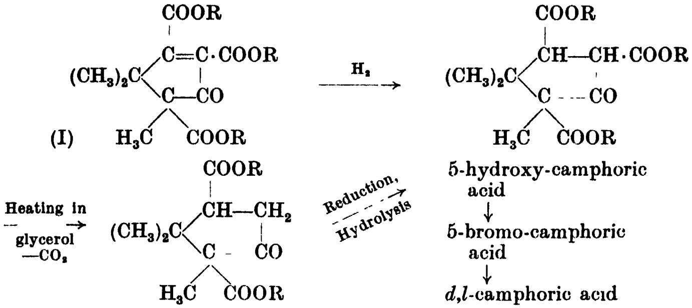
m.p. (active) 107°, (*dl*) 109°, b.p. 255°, is formed by heating camphor, borneol or isoborneol with caustic potash to 250–280° (*Guerbet*, Bull. **11** [1894], 610; C. r. **148**, 720). It is oxidised by boiling nitric acid to camphoric and camphoronic acids (*Guerbet*, Bull. **11** [1894], 426); camphoric acid can be reconverted into campholic acid by reducing the anhydride to α-campholide (p. 310), converting this with HBr into bromocampholic acid, and heating the latter with Zn dust to 50–60° (*Haller* and *Blanc*, C. r. **130**, 415). Cf. also benzylidene-campholic acid, p. 299. *Anhydride*, m.p. (active) 58°, (*dl*) 66°. The *chloride*, b.p. 222°, decomposes, when heated with P_2O_5, into HCl, CO and campholene (p. 301), and gives with CH_3MgI the ketone  $C_8H_{14}{<}\begin{smallmatrix}CH_3\\ COCH_3\end{smallmatrix}$, b.p. 102°/18 mm., *semicarbazone* m.p. 232° (*Meerwein*, Ann. **417**, 270). *Campholic amide* has m.p. (active) 79°, (*dl*) 90°. The *nitrile*, m.p. 72°, b.p. 218°, gives *campholamine*, $C_{10}H_{19}NH_2$, b.p. 210°, on reduction. The amide gives *camphelyl isocyanate*, b.p. 201°, with Br and alkali, from which *camphelamine*, $C_9H_{17}NH_2$, m.p. 43°, b.p. 175°, can be obtained (*Errera*, Gazz. **23** II 497, 500; *v. Braun*, Ann. **490**, 126; *Knoll* and *Schmidt*, Germ. Pat. 544,890 [1930]). The reduction of campholic ester with Na and alcohol gives *camphol alcohol* $C_9H_{17}\cdot CH_2OH$, m.p. 60°, b.p. 213°, the *p-nitrobenzoate* of which, m.p. 95°, has a strong smell of flowers (*Rupe* and *Fehlmann*, Helv. **9**, 80, 97). This campholic alcohol is different from the *tertiary campholic alcohol*, b.p. 203°, formed by the action of silver nitrite on campholamine hydrochloride; in the latter reaction, the five-membered ring is enlarged to a six-membered ring (*Bredt*, J. pr. **96**, 70; cf. also *v. Braun* and *Anton*, Ber. **66**, 1377). **Dimethylcampholic acid,** m.p. 74°, is obtained in the form of its *amide*, m.p. 82°, by the action of $NaNH_2$ on dimethyl-camphor (*Haller* and *Ramart*, C. r. **178**, 682; *v. Braun* and *Kurtz*, Ber. **67**, 229).

In the preparation of campholic acid a saturated, isomeric acid is formed as a by-product; this is **isocampholic acid,** $C_{10}H_{18}O_2$, and it can be separated from campholic acid by repeated esterification and hydrolysis: b.p. 141°/9 mm.; *anilide*, m.p. (active) 119·5°, (*dl*) 137–139°. It can be degraded thus: $C_8H_{15}\cdot CH_2\cdot COOH \rightarrow C_8H_{15}\cdot CH_2\cdot CH_2OH \rightarrow C_8H_{15}CH{:}CH_2 \rightarrow C_8H_{15}CHO \rightarrow C_8H_{15}COOH$ to the **lower homologue of isocampholic acid,** *ethyl amide* m.p. 69° (*v. Braun* and *Heymons*, Ber. **61**, 2280; *v. Braun* and *Anton*, Ber. **66**, 1376), so that it must be formulated as 1:2:2-trimethylcyclopentane-3-acetic acid (α-campholanic acid); see, however, *Lipp*, Ber. **55**, 1883; see also its formation from campholic acid, *Rupe* and *Briellmann*, Helv. **5**, 767.

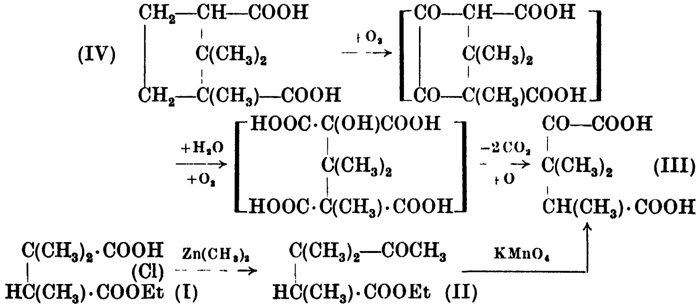
Camphoric acid, and its **reaction-** and **degradation products** (for nomenclature, see *Bredt*, Ann. **395**, 35). — Camphoric acid was discovered by *Kosegarten* as early as 1785; its composition was shown to be $C_{10}H_{16}O_4$ by *Malaguti* in the year 1837. The constitutional formula for camphoric acid was proposed by *J. Bredt* in 1893 in connection with his formula for camphor. Camphoric acid contains two asymmetric carbon atoms, and all the forms theoretically possible are known, viz. four optically active and two racemic forms, *d*,cis- and *l*,cis-, *d*,trans- and *l*,trans-, and *dl*-cis- and *dl*-trans-camphoric acids.

d,cis-**Camphoric acid** (IV, p. 305), m. p. 187°, $[\alpha]_j^{16\cdot5} + 49\cdot7°$ (in alcohol, $p = 10$), is formed by heating *d*-camphor or campholic acid with nitric acid (*Wreden*, Ann. **163**, 323; *Bredt*, Ber. **26**, 3050), and by the oxidation of borneol, isoborneol, camphor quinone, bornylene and epicamphor; it has been investigated in detail, because it is so easily obtained. When heated above its melting point or treated with acetyl chloride (*Anschütz*, Ann. **226**, 1) it is converted into its *anhydride*, m.p. 221°, b.p. 270°. The first synthesis of camphoric acid was carried out by *Komppa*; see p. 284. Further syntheses have been worked out by *Perkin jun.* and *Thorpe* and by *Toivonen.*

Not all the stages of the synthesis of *Perkin* and *Thorpe* (J. **89**, 795) have been explained, and the final yield is very small. The synthesis of *Toivonen* (C. 1927 II 1248; 1936 II 4013) is worthy of notice, because it shows the structure of the condensation product of αα′-dibrom-ββ-dimethylglutaric ester and sodio-malonic ester (p. 164, formulae I and II); this must be formulated as a cyclopentene derivative, since treatment with Na and CH_3I gives 2:3:3-trimethyl-Δ^4-cyclopentenone-2:4:5-tricarboxylic ester (I, below). That this formula is correct is shown by the degradation of the compound via γ-acetyl-γγ-dimethylpropane-αβ-dicarboxylic acid (III; p. 164) to αα-dimethyltricarballylic acid, and by its conversion into cis- and trans-*dl*-camphoric acid by the following stages:



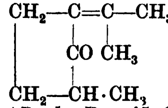
The fusion of camphoric acid with sodium or potassium hydroxide gives a number of volatile acids, such as isopropyl-succinic acid, dihydrocamphoric acid, $HOOC \cdot CH(CH_3) \cdot CH_2 \cdot CH_2 \cdot CH(COOH) \cdot CH(CH_3)_2$, pseudo-camphoric acid and various other acids not yet investigated (*Crossley* and *Perkin jun.*, J. **73**, 1). Oxidation with nitric acid yields camphoronic acid, a dinitrocaproic acid $\begin{array}{l}(CH_3)_2C \cdot CO_2H \\ | \\ CH_3 \cdot C(NO_2)_2\end{array}$, dimethylmalonic acid, succinic acid and oxalic acid (*Bredt*, Ber. **27**, 2092); chromic acid yields camphoronic acid and trimethylsuccinic acid (*Bredt*, Ber. **26**, 3048); bromine water gives camphanic acid (p. 309) (*Mahla* and *Tiemann*, Ber. **28**, 2151). The oxidation of camphoric acid with permanganate yields oxalic acid and the characteristic dibasic γ-keto-$\alpha\beta\beta$-trimethylglutaric acid $C_8H_{12}O_5$ (III), m.p. 121° (*Balbiano's* acid: *Mahla* and *Tiemann*, Ber. **28**, 2159), which can be resolved into optical antimers, and can be reduced with hydriodic acid to $\alpha\beta\beta$-trimethylglutaric acid. Its formation can be explained in the following manner:



Balbiano's acid (III) has been synthesised from the chloride (I) of the semi-ester of trimethylsuccinic acid (*Bardhan*, J. **1928**, 2604); when this reacts with $Zn(CH_3)_2$, the product is the ester of $\alpha\beta\beta$-trimethyl-laevulinic acid (II), which is oxidised to γ-keto-$\alpha\beta\beta$-trimethylglutaric acid (III).

The distillation of the Ca salt of camphoric acid yields **camphorone**,

camphor-phorone

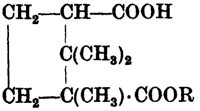


b.p. 83°/10 mm., *semicarbazone* m.p. 198°, *oxime* m.p. 115° (*Bredt*, Ber. **45**, 3818); thus there is not only formation of a cyclic ketone (p. 20), but also fission of the camphor bridge (p. 300). The structure first given to camphorone because of its oxidation products, formic, acetic and methylglutaric acids was established by its synthesis from

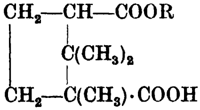
2-methylcyclopentanone (p. 55) and acetone with sodium ethoxide (*Bouveault*, C. r. **130**, 415), and by its decomposition into these substances when heated with caustic potash (*Wallach*, Ann. **331**, 322) (cf. also the degradation of camphorone with ozone, giving α-methylglutaric acid and acetone: *Kon* and *Nutland*, J. **1926**, 3109). Its constitution is also supported by its behaviour with hydroxylamine, with which it gives an addition product, *camphorone-hydroxylamine*, $C_9H_{15}O(NHOH)$, m.p. 120° (*Harries* and *Matfus*, Ber. **32**, 1343; cf. *Sanna*, Gazz. **59**, 232). Reduction with Na and alcohol leads to a secondary alcohol, **dihydrocamphorol**, $C_9H_{17}OH$; oxidation of this with CrO_3 gives **dihydrocamphorone,** $C_9H_{16}O$, b.p. 184–185° (p. 56) (*Semmler*, Ber. **37**, 236), which is identical with **dihydro-pulegenone** (p. 236), and has been synthesised from α-methyl-α′-isopropyl-adipic acid.

Tetra- and hexa-hydro-isoxylenes (pp. 90, 95) are formed by heating camphoric acid with hydriodic acid.

When camphoric acid is esterified with alcohols and a mineral acid, only small quantities of the neutral esters are formed. In agreement with its formula, camphoric acid forms two series of acid esters: 1. the **tert.-sec.-ester-acids** (α- or *ortho*-) (I); these are obtained by partial hydrolysis of the neutral esters; 2. the **sec.-tert.-ester-acids** (*β*- or *allo*-) (II), which are formed by partial esterification of the acid (*Bruhl*, Ber. **26**, 289; *Bredt*, *ib.* **26**, 3050; Ch. Ztg. **20**, 843; J. pr. **83**, 399; **84**, 788; **133**, 92; Ann. **328**, 339; *Anschütz*, Ber. **30**, 2654; *Loir*, Ann. chim. phys. **38** (1853), 483). This behaviour of the camphoric esters on hydrolysis and of camphoric acid on esterification is due to the different reactivities of the two carboxyl groups, which are caused by their respective positions in the molecule. *Dimethyl ester*, b.p. 142·8°/17·5 mm.; α- or ortho-*methyl hydrogen camphorate*, m.p. 77°; *β*- or allo-*methyl hydrogen camphorate*, m.p. 86–87°; *Diethyl ester*, b.p. 157·4°/16·5 mm.; *mono-esters*: ortho-, m.p. 47–48·5°; allo-, m.p. 56°. For the electrolysis of the ester-acids see *Walker*, Ber. **26**, 600; J. **1892**, 1088; *Haller*, C. r. **116**, 121; *Hoogewerff* and *van Dorp*, Rec. **12**, 23. For derivatives of the ester-acids see *Haller* and *Blanc*, C. r. **141**, 697.



(I)

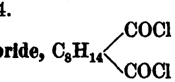


(α) (*ortho*) (secondary)

(*β*) (*allo*) (tertiary).

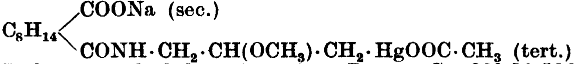
(II)

Camphoric acid is an antiseptic and reduces perspiration. A number of its salts and esters have been recommended for medical use; e.g. the acid salt of pyramidone and camphoric acid, $C_{13}H_{17}N_3O + C_{10}H_{16}O_4$, and the corresponding neutral salt, $2\,C_{13}H_{17}N_3O + C_{10}H_{16}O_4$, in which the effect of camphoric acid in reducing perspiration is united with the antipyretic effect of pyramidone. "*Amphotropin*", the hexamethylene-tetramine (hexamine) salt of camphoric acid, $2\,C_6H_{12}N_4 + C_{10}H_{16}O_4$, has been much used as an internal urinary antiseptic (C. 1912 II 1844; Germ. Pat. 270,180 [1911]; *Remete*, C. 1931 I 1477). For other salts see *Kahlbaum*, Germ. Pat. 519,053 (1926); *Rojahn*, Germ. Pat. 582,805 (1931); *Keteszty* and *Wolf*, Brit. Pat. 447,877 (1935). "*Camphosan*" is the methyl-santalyl-ester (*Riedel*, Germ. Pat. 208,637 [1908]); "*camphoral*" is the di-santalyl-ester (*Riedel*, Germ. Pat. 193,960 [1906]); "*guacamphol*" is the di-guaiacol-ester, m.p. 126–127° (*Grohmann*, Pharm. Ztg. **50**, 158). For the Bi salt, see *Lauter* and *Braun*, J. Am. pharm. Ass. **25**, 394.

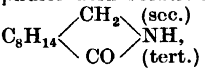
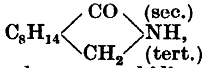
Camphoric dichloride,  $C_8H_{14}\begin{cases}COCl\\COCl\end{cases}$ (*Scheiber* and *Knothe*, Ber. **45**, 2254); the cis-form rearranges on distillation into the trans-form, b.p. 140°/15 mm. (*Bredt*, Ber. **28**, 319 note). **α-Chlorocamphoric acid dichloride,** b.p. 149°/12 mm., m.p. 26°, is formed by heating camphoric anhydride with PCl_5 for 20 hours (*Bredt*, Ber. **45**, 1426), and gives with H_2O *chlorocamphoric* *anhydride*, m.p. 235°. α-**Bromocamphoric acid chloride** has b.p. 175°/15 mm., and *α-bromocamphoric anhydride* has m.p. 196°.

The **diamide,** $C_8H_{14}(CONH_2)_2$, cis, m.p. 197–199°, is formed from camphorylmalonic ester with NH_3; trans. m.p. + 1 H_2O 132°; anhydrous 160°, is formed from trans-camphoric acid dichloride and NH_3 (*Bredt*, Ber. **45**, 1421).

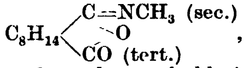
Camphoric half-amide half-acids: the **sec.-tert.-compound** (α)-[1] m.p. 177°, is formed from isonitroso-camphor and HCl and also from camphoric anhydride and ammonia, together with the **tert.-sec.-compound** (β-), m.p. 182°; the latter is also formed from camphorimide and caustic soda. Distillation of the Ca salt with soda-lime gives the nitrile of *2:6-dimethyl-Δ⁵-heptenoic acid*, $(CH_3)_2\cdot C{:}CH\cdot CH_2\cdot CH_2\cdot CH(CH_3)\cdot CN$ (*Bredt*, Ann. **328**, 338). For degradation products of these two acids, see p. 310. "*Novurite*" is a solution of 5% of theophylline and 10% of a tert.-sec.-camphor-amide-acid derivative, the methoxy-allylamino-mercuric acetate derivative of camphoric acid

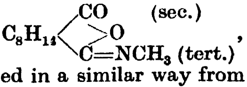

$C_8H_{14}\left<\begin{array}{l}\text{COONa (sec.)}\\ \text{CONH}\cdot CH_2\cdot CH(OCH_3)\cdot CH_2\cdot HgOOC\cdot CH_3\ \text{(tert.)}\end{array}\right.$

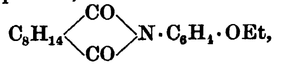
It has a marked diuretic action (*Popper*, C. 1929 II 596; *Zernik*, C. 1929 I 2345; *Hahn*, C. 1930 I 1415; *Müllern*, C. 1930 I 3459; etc.).

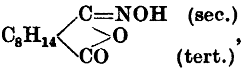
Camphoric imide, $C_8H_{14}(CO)_2NH$, m.p. 248°, b.p. 300°, is formed from camphoric anhydride by distillation in a stream of NH_3, and from isonitroso-camphor by rearrangement (*Angeli*, Ber. **26**, 58; *Manasse*, *ib.* 242; *Winzer*, Ann. **257**, 308; *Bredt*, *ib.* **328**, 342). Camphoric imide is reduced at a lead electrode in sulphuric acid solution to give two isomeric lactams, α- and **β-camphidones,**  $C_8H_{14}\left<\begin{array}{l}CH_2\ \text{(sec.)}\\ CO\ \text{(tert.)}\end{array}\right>NH$, m.p. 231°, b.p. 295°;  $C_8H_{14}\left<\begin{array}{l}CO\ \text{(sec.)}\\ CH_2\ \text{(tert.)}\end{array}\right>NH$, m.p. 228°, b.p. 308°. Further reduction gives the base **camphidine,** $C_8H_{14}(CH_2)_2NH$, m.p. 186°, b.p. 209° (*Tafel* and *Eckstein*, Ber. **34**, 3274). α- and β-Camphidone are the lactams of α- and β-amino-campholic acids (p. 308), and the hydrochlorides of the latter give the camphidones on distillation (*Rupe* and *Splittgerber*, Ber. **40**, 4311). Nitroso-α-camphidone is converted into α-campholide (p. 310) by warming with alkali (*Tafel* and *Bublitz*, Ber. **38**, 3806); when α-campholide is heated under pressure with the zinc chloride-ammonia complex, it is reconverted into camphidone (*Schroeter*, Ber. **53**, 1917). For **thiocamphoric imide,** $C_8H_{14}(CS)_2NH$, m.p. 135°, see *Oddo* and *Mannessier*, Gazz. **40** I, 43.

N-Methyl-camphoric imide, $C_8H_{14}(CO)_2NCH_3$, m.p. 41°, is formed by heating the silver salt of camphorimide with methyl iodide, and also by heating the α-methyl-iso-imide above its melting point (*Hoogewerff* and *van Dorp*, Rec. **12**, 22; **14**, 252).

α-**Camphoric methyl-isoimide,**  $C_8H_{14}\left<\begin{array}{l}C{=}NCH_3\ \text{(sec.)}\\ CO\ \text{(tert.)}\end{array}\right>O$, m.p. 136°, from α-(*ortho*-)camphoric mono-methylamide and acetyl chloride or PCl_3 (*Hoogewerff* and *van Dorp*, Rec. **12**, 22), changes into N-methyl camphoric imide when heated above its m.p.

β-**Camphoric methyl-isoimide,**  $C_8H_{14}\left<\begin{array}{l}CO\ \text{(sec.)}\\ C{=}NCH_3\ \text{(tert.)}\end{array}\right>O$, m.p. 86°, b.p. 258° (without rearrangement), is formed in a similar way from β-(*allo*-)camphoric mono-methylamide, m.p. 178°, obtained from the methylimide and NaOH.

Camphoric phenetidide,  $C_8H_{14}\left<\begin{array}{l}CO\\ CO\end{array}\right>N\cdot C_6H_4\cdot OEt$, m.p. 119°, is used as an antipyretic and for reducing perspiration.

Camphoric-α-hydroximic acid anhydride,  $C_8H_{14}\left<\begin{array}{l}C{=}NOH\ \text{(sec.)}\\ CO\ \text{(tert.)}\end{array}\right>O$, m.p.

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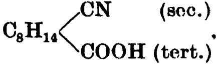
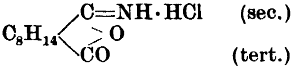
[1] For the meaning of α and β, see the formulae on p. 306.

225°, is prepared by boiling nitrocamphor with HCl (*Perkin jun.*, J. **73**, 798), and from hydroxylamine and camphoric anhydride (*Errera*, Gazz. **24** II, 342).

α-Camphoric acid semi-nitrile, *cyanolauronic acid,*  $\mathrm{C_8H_{14}}<\begin{matrix}\mathrm{CN}\ \ (\text{sec.})\\ \mathrm{COOH}\ (\text{tert.})\end{matrix}$, m.p. 152°, is formed by the action of acetic anhydride or PCl_5 upon isonitroso-camphor, and by heating isonitroso-camphor to 206–207° (*Sernagiotto*, C. 1918 II 276); it is also obtained from cis-camphoric acid dichloride and ammonia (*Bredt*, Ber. **45**, 1422). In ethereal solution it absorbs HCl to form the *hydrochloride* of *camphoric iso-imide*,  $\mathrm{C_8H_{14}}<\begin{matrix}\mathrm{C{=}NH\cdot HCl}\ \ (\text{sec.})\\ >\mathrm{O}\\ \mathrm{CO}\ \ (\text{tert.})\end{matrix}$

α-Camphoric semi-nitrile acid *chloride*, m.p. 99°, b.p. 153–155°/15 mm. (*Borsche* and *Sander*, Ber. **48**, 119) is formed from PCl_5 and camphoric imide, or from camphoric semi-nitrile acid and thionyl chloride; by further action of PCl_5 the H-atom next to the nitrile group is substituted, giving **α-chloro-camphoric acid semi-nitrile chloride,** which is converted into **α-chloro-camphoric imide** by warming with HCl (*Breat* and *Iwanov*, Ber. **58**, 58; *Bredt*, *ib.* 63). **β-Camphoric acid semi-nitrile,** m.p. 111°, is formed from β-camphoric mono-amide. If the Ca salt of either acid is distilled, the ring is opened to form the *nitrile*, b.p. 89–90°/14 mm., of the dimethyl-heptenoic acid which is also obtained by the distillation of camphoric imide or camphoric mono-amide with lime (see above). This nitrile is the lower homologue of citronellic nitrile (p. 206) (*Bredt*, Ann. **328**, 338). α- and β-Camphoric semi-nitriles are reduced by sodium and alcohol to α- and **β-aminocampholic acids,** $C_8H_{14}(CH_2NH_2)COOH$; their *hydrochlorides*, m.ps. (α-) 248°, (β-) 215–222°, are converted by heat into α- and β-camphidones (see above) (*Rupe* and *Splittgerber*, Ber. **40**, 4311). **cis-Camphoric dinitrile,** m.p. 160°, is formed from the nitrile of camphoric mono-amide, m.p. 130°, by treatment with PCl_5 (*Bredt*, Ber. **45**, 1428); the **trans-dinitrile,** m.p. 145°, is obtained by dehydration of the trans-diamide (see above). Both nitriles are reduced with Na and alcohol to the corresponding diamines (*Bredt* and *de Souza*, J. pr. **133**, 84).

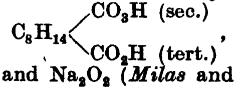
l,cis-**Camphoric acid,** $[\alpha]_{\mathrm{D}}^{17}$ — 49·5° (in alcohol, p = 9·83), is prepared by the oxidation of *l*-camphor or *l*-borneol, and is identical with *d*,cis-camphoric acid in every respect save the direction of its optical rotation.

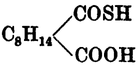
dl,cis-**Camphoric acid,** *paracamphoric acid,* m.p. 204°, is formed by mixing alcoholic solutions of equimolecular quantities of *d*-cis- and *l*-cis-camphoric acids (*Marsh*, Chem. News **60**, 307), and by the oxidation of *dl*-camphor. For the resolution of *dl*-cis-camphoric acid, see *Beckmann* (Ber. **42**, 487). Its *anhydride* has m.p. 221°.

d-**Isocamphoric acid,** *d,trans-camphoric acid,* m.p. 171°, $[\alpha]_{\mathrm{D}}^{20}$ + 48·6° (in alcohol, p = 9·88); when *l*,cis-camphoric acid is heated with water or, better, with a mixture of acetic acid and HCl, it is partly converted into this acid, which does not form an anhydride, and it can thus be readily separated from the *l*,cis-camphoric acid by means of acetyl chloride (cf. p. 304); the action of heat, however, converts it into the anhydride of *l*,cis-camphoric acid.

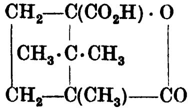
l-**Isocamphoric acid,** $[\alpha]_{\mathrm{D}}^{15}$ — 48·9° (in alcohol, p = 10), is formed in the same way from *d*,cis-camphoric acid. The action of water on the chloride of *d*,cis-camphoric acid gives a mixture of this acid and *d*,cis-camphoric acid.

dl-**Isocamphoric acid,** m.p. 191°, is obtained by mixing *d*- and *l*-iso-camphoric acids. *dl*-Isocamphoric acid gives *dl*-camphoric anhydride when heated (*Aschan*, Ber. **27**, 2001). For the crystalline form of the camphoric acids, cf. *Walden*, Ber. **29**, 1700. For **3-methyl-camphoric acid** see *Bredt-Savelsberg*, Ber. **65**, 1; for **3-phenyl-camphoric acid** see *Nametkin*, *Kitchkin* and *Kurssanov*, J. pr. **124**, 144; *Bredt-Savelsberg* and *Buchkremer*, Ber. **66**, 1921.

Percamphoric acid,  $\mathrm{C_8H_{14}}<\begin{matrix}\mathrm{CO_3H}\ (\text{sec.})\\ \mathrm{CO_2H}\ (\text{tert.})\end{matrix}$, m.p. 49–50°, is prepared from camphoric anhydride and Na_2O_2 (*Milas* and *McAlevy*, Am. **55**, 349, 352).

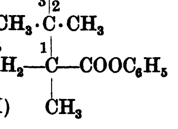
Thiocamphoric acid, $C_{10}H_{16}O_3S$, 
$C_8H_{14}<\begin{smallmatrix}COSH\\COOH\end{smallmatrix}$, is obtained from camphoric anhydride and a solution of Na disulphide; it is a liquid with a smell of leeks. The Na salt is known as "*camphostyl*" (*Regnier* and *Vleeschhouwer*, C. 1935 II 2237).

Camphanic acid,

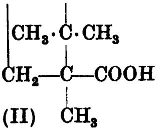


m.p. 201°, is formed from α-chloro- and α-bromo-camphoric anhydrides by boiling with water. It is oxidised by nitric and chromic acids to camphoronic acid (*Bredt*, Ber. **18**, 2989). When distilled, it decomposes into laurolenic acid (p. 311) and *laurololactone*, m.p. 50°, with loss of CO_2 (*Fittig* and *Woringer*, Ann. **227**, 1; *Bredt*, J. pr. **88**, 400; **87**, 1). For the degradation of camphanic nitrile to **camphononic acid,** *2:2:3-trimethyl-cyclopentanone-3-carboxylic acid*, m.p. 229°, see *Bredt*, *Lund* and *Amann*, J. pr. **84**, 790. **Apocamphononic acid,** m.p. 110°, has been synthesised (*Perkin jun.* and *Thorpe*, J. **85**, 128). ω-**Bromo-camphoric acid,** m.p. 208–209° (decomp.), is the product of the oxidation of ω-bromocamphor and ω:2-dibromocamphane with nitric acid (*Lipp* and *Lausberg*, Ann. **436**, 283); its *anhydride* has m.p. 149–149·5°. For π-**bromo-** and π-**hydroxy-camphoric acids,** see *Kipping*, Proc. **1895**, 88, 210; J. **69**, 913; **75**, 125.

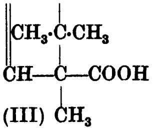
Dehydro-camphoric acid (II), m.p. (active) 202–203°, (*dl*) 228°; [α]D + 113·8° (7·83% solution in ethyl alcohol) (*Bredt*, *Houben* and *Levy*, Ber. **35**, 1286; *Bredt*, Ann. **395**, 26), is prepared by heating *chlorocamphoric acid diphenyl ester* (I), m.p. (active) 89°, (*dl*) 74°, with quinoline, followed by hydrolysis of the *dehydro-camphoric acid diphenyl ester*, m.p. (active) 155°, (*dl*) 133°. Dehydro-camphoric acid *chloride* has m.p. 50°, the *diamide* has m.p. 191°. Dehydro-camphoric acid itself forms no anhydride, but on distillation the double bond migrates from the $\Delta^{3:4}$-position to the $\Delta^{4:5}$-position, with the formation of the *anhydride* of *isodehydro-camphoric acid* (III), m.p. 184° (*acid*, m.p. 181°) (*Bredt's Rule*: Ann. **437**, 1, 13); camphonenic acid (IV) is also formed by loss of CO_2. The oxidation of dehydro-camphoric acid yields camphoronic acid. The addition of HBr leads to a mixture of **4-bromo-trans-camphoric acid,** m.p. (active) 232°, (*dl*) 240°, and **4-bromo-cis-camphoric acid** (V), m.p. (active) 160°, (*dl*) 140°, which on reduction give the corresponding stereoisomeric camphoric acids. When the Na salt of 4-bromo-trans-camphoric acid is heated in aqueous solution, the Br is replaced by OH, giving **4-hydroxy-trans-camphoric acid** (VI); camphonenic acid (IV) is also formed. Under the same conditions, 4-bromo-cis-camphoric acid yields the **lactone** of **4-hydroxy-camphoric acid** (VII), m.p. 228° (*Komppa*, Ann. **370**, 225):



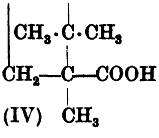
(I)



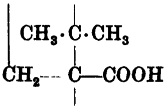
(II)



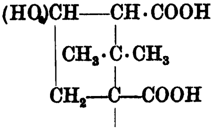
(III)



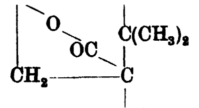
(IV)



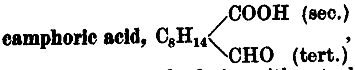
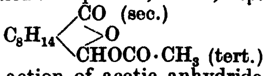
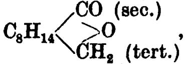
(V)

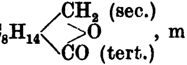
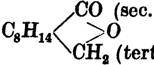


(VI)



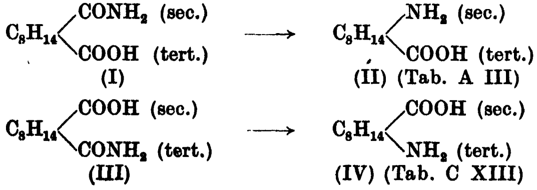
(VII)

The semi-aldehyde of camphoric acid,  $C_8H_{14}<\begin{matrix}\text{COOH (sec.)}\\ \text{CHO (tert.)}\end{matrix}$, m.p. (active) 78°, (*dl*) 64°, is formed from camphor quinone by fusion with potash; *oxime*, m.p. (active) 155°, (*dl*) 149°. **Acetoxy-β-campholide,**  $C_8H_{14}<\begin{matrix}\text{CO (sec.)}\\ \text{CHOCO}\cdot\text{CH}_3\text{ (tert.)}\end{matrix}>O$ is obtained in two stereoisomeric forms by the action of acetic anhydride on the semi-aldehyde; they have m.ps. (active) 128°, (*dl*) 98°, and (active) 83°, (*dl*) 74°. The electrolytic reduction of the semi-aldehyde yields **β-campholide,**  $C_8H_{14}<\begin{matrix}\text{CO (sec.)}\\ \text{CH}_2\text{ (tert.)}\end{matrix}>O$, m.p. (active) 219°, (*dl*) 217° (see below) (*Bredt,* J. pr. **95**, 63; **96**, 67).

α-Campholide,  $C_8H_{14}<\begin{matrix}\text{CH}_2\text{ (sec.)}\\ \text{CO (tert.)}\end{matrix}>O$, m.p. 211°, is prepared by the reduction of camphoric anhydride with Na and alcohol, or H_2 and Ni at 210° (*Rupe* and *Jäggi,* Helv. **3**, 654), and by warming nitroso-α-camphidone (p. 307) with alkali, methods which are similar to the preparation of phthalide from phthalic anhydride or nitroso-phthalimidine (*Haller,* C. r. **122**, 293, 446); it is also obtained by the oxidation of camphor with Caro's acid (*Baeyer* and *Villiger,* Ber. **32**, 3630). With PCl_5 it gives *chlorocampholic acid chloride*, $C_8H_{14}(CH_2Cl)COCl$, m.p. 21°, b.p. 132°/15 mm. Treatment with HBr yields *bromocampholic acid,* $C_8H_{14}(CH_2Br)COOH$, m.p. 177° (decomp.), which can be reduced to campholic acid (p. 303), and which is converted by PCl_5 into bromocampholic acid *chloride,* m.p. 37°, b.p. 147°/15 mm. **β-Campholide,**  $C_8H_{14}<\begin{matrix}\text{CO (sec.)}\\ \text{CH}_2\text{ (tert.)}\end{matrix}>O$, (*see above*) *is formed in poor yield by the reduction of* the tert.-sec.-methyl ester of camphoric acid with Na and alcohol (*Haller* and *Blanc,* C. r. **141**, 697; cf. *Rupe* and *Splittgerber,* Ber. **40**, 4311), but a good yield is obtained by the electrolytic reduction of the semi-aldehyde of camphoric acid (see above). Dialkyl-α-campholides, such as *dimethyl-* and *diethyl-α-campholide,* b.p. 146°/10 mm. and m.p. 38° respectively, are prepared by the action of alkyl Mg halides upon camphoric acid esters or camphoric anhydride; when the latter is used, the corresponding β-campholide is also formed: *dimethyl-β-campholide* has m.p. 84° (*Shibata,* J. **97**, 1239).

Camphoric acid can be degraded in two different ways, since either the secondary or the tertiary carboxyl group can be removed from the molecule. The degradation products formed by the first method belong to the camphonanic series, if no rearrangement has taken place (table A, pp. 312, 313), but when a methyl group has migrated they belong to the laurolanic series (table B). The products formed by the second method of degradation are derivatives of the α-campholytic series (table C) if there has been no rearrangement, of the β-(or iso-)campholytic series if a methyl has wandered (table D).

The camphoric-amide-acids, (I) and (III), form the starting materials for these degradations; when treated with bromine and alkali, they give two isomeric amino-acids, **aminocamphonanic acid** (II), and **amino-dihydro-α-campholytic acid** (IV):



$$C_8H_{14}<\begin{matrix}\text{CONH}_2\text{ (sec.)}\\ \text{COOH (tert.)}\end{matrix} \longrightarrow C_8H_{14}<\begin{matrix}\text{NH}_2\text{ (sec.)}\\ \text{COOH (tert.)}\end{matrix}$$

(I) (II) (Tab. A III)

$$C_8H_{14}<\begin{matrix}\text{COOH (sec.)}\\ \text{CONH}_2\text{ (tert.)}\end{matrix} \longrightarrow C_8H_{14}<\begin{matrix}\text{COOH (sec.)}\\ \text{NH}_2\text{ (tert.)}\end{matrix}$$

(III) (IV) (Tab. C XIII)

Aminocamphonanic acid (table A, III) (also known as *amino-dihydrolauronolic acid* and *amino-lauronic acid*) gives with acetic anhydride the **lactam** (table A, IV). The nitroso derivative of this compound gives on boiling with alkali **camphonolic lactone** (table A, VI), and a product of the migration of a methyl group, **laurololactone** (table B, XI) (also known as dihydrolaurolactone and isocampholactone), m.p. 32°. **Amino-dihydro-α-campholytic acid** (table C, XIII), which can also be prepared from the chlorimide of camphoric acid and Na ethoxide, similarly forms a **lactam** with ease (table C, XIV), and also a lactone, **dihydro-hydroxy-campholytolactone** (table C, XVI), m.p. 116° (*Bredt*, *Rochussen* and *Monheim*, Ann. **314**, 392). The replacement of both COOH-groups in camphoric acid by NH_2 with the aid of N_3H leads to **1:3-diamino-2:2:3-trimethyl-cyclopentane**, m.p. 124°, *picrate* m.p. 256° (*Knoll* and *Schmidt*, Germ. Pat. 544,890 [1930]).

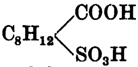
Camphonenic acid (table A, II) (also known as *γ-lauronolic* or allo-*campholytic acid*), m.p. 156°, b.p. 130–133°/22 mm. (*Bredt*, J. pr. **87**, 8), is formed from amino-camphonanic acid (table A, III) and nitrous acid, and from dehydro-camphoric acid (table A, I) by loss of CO_2; it is also obtained by removal of HBr from 3-bromocamphonanic acid (table A, V) with Na_2CO_3; it is oxidised at the double bond by $KMnO_4$ or HNO_3 to form camphoronic acid (p. 314). Other members of the camphonanic series are **camphonolic acid** (table A, VII), which is obtained in cis and trans forms by the electrolytic reduction of **camphononic acid** (table A, VIII); the cis-form is readily converted into **camphonolic lactone** (table A, VI), which adds HBr to give **3-bromocamphonanic acid** (table A, V). The latter is easily reconverted into camphonolic lactone (*Bredt*, J. pr. 84, 797).

Laurolenic acid (table B, X) (also known as *isolauronic acid* or *Woringer's lauronolic acid*), b.p. 240°, 135°/15 mm. (*Bredt*, J. pr. **83**, 395), is obtained by the distillation of camphanic acid, and from bromocamphoric anhydride and sodium carbonate; it is also formed from 3-bromocamphonanic acid (table A, V) by treatment with KOH (*Bredt* and *Amann*, J. pr. 87, 13). HCl converts camphonenic acid and laurolenic acid into the same γ-lactone, laurololactone (table B, XI) (previously known as *campholactone* or *iso-dihydro-laurolactone*), m.p. 50°, which is a stereoisomer of the laurololactone of m.p. 32° (previously named *dihydrolaurolactone*) (*Bredt*, J. pr. **83**, 400).

α-Campholytic acid (table C, XII), is a liquid, b.p. 140°/15 mm, formed by the action of nitrous acid on amino-dihydro-α-campholytic acid (table C, XIII); *hydroxy-dihydro-α-campholytic acid* (table C, XV), $C_8H_{14}(OH)COOH$, m.p. 132°, and its *lactone*, m.p. 116° (table C, XVI), are by-products in this reaction. It is also obtained by the electrolysis of the K salt of the sec.-methyl ester of camphoric acid (p. 306). It is oxidised by nitric acid to *dimethyltricarballylic acid*, $HOOC \cdot C(CH_3)_2 \cdot CH(COOH) \cdot CH_2COOH$ (*Tiemann*, Ber. **33**, 2935); for further oxidation products, see *Chandrasena*, *Ingold* and *Thorpe*, J. **127**, 1677. Just as α-campholenic acid changes into β-campholenic acid (p. 301) (*Bredt*, *Rochussen* and *Monheim*, Ann. **314**, 391; *Walker* and *Cormack*, J. **77**, 374), so α-campholytic acid rearranges in presence of dilute sulphuric acid into

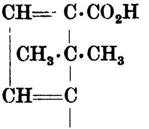
β-Campholytic acid (table D, XVIII), m.p. 134°; this was previously known as *isolauronolic acid* and is also formed from camphoric anhydride and aluminium chloride (cf. *Lees* and *Perkin jun.*, Proc. **16**, 18; J. **79**, 332), and by heating sulphocamphylic acid (table D, XIX) to 200°. Its nitrile is obtained from α-camphoric-semi-nitrile acid chloride and aluminium chloride (*Salmon-Legagneur*, C. r. **200**, 1222). With hot conc. sulphuric acid β-campholytic acid gives sulphocamphylic acid once more. β-Campholytic acid does not contain an asymmetric carbon atom, and hence is optically inactive. Its *amide* has m.p. 129–130°. As with β-campholenic acid, oxidation with chromic acid gives *acetyl-isocaproic acid*, $CH_3 \cdot CO \cdot C(CH_3)_2 \cdot CH_2 \cdot CH_2 \cdot COOH$ (p. 302) and *αα-dimethylglutaric acid* (*Blanc*, Ann. chim. phys. (7) **18**, 181; Bull. **21** (1899), 854; cf. *Bredt*, *Rochussen* and *Monheim*, Ann. **314**, 392).

For a synthesis of α-campholytic and β-campholytic acids from 1:1-dimethylbutane-1:2:4-tricarboxylic acid, etc., see *Perkin jun.* and *Thorpe*, Proc. **19**, 61; J. **85**, 128. For the degradation of dihydro-α- and -β-campholytic acids to 2:2:3- and 2:3:3-trimethylcyclopentanones, respectively, see *Noyes* and *Patterson*, Am. **27**, 425; *Bouveault* and *Blanc*, C. r. **136**, 1460.

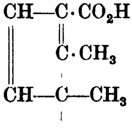


$C_8H_{12}\begin{matrix}COOH\\SO_3H\end{matrix}$

Sulphocamphylic acid (table D, XIX), $C_8H_{12}(COOH)(SO_3H) + 3\,H_2O$, m.p. 165° (decomp.), is obtained by the action of sulphuric acid on camphoric acid. It loses two molecules of water of crystallisation at 100°, but the third is lost only at 110°, a fact which may indicate that it enters into the constitution of the molecule. Heating converts it into β-campholytic acid; fusion with caustic soda gives two acids, $C_9H_{12}O_2$, α- and **β-camphylic acids**, m.ps. 148° and 106°; the α-acid is reduced by Na amalgam (*Perkin jun.*, J **83**, 835) to inactive α-campholytic acid (see above; cf. also *Noyes* and *Patterson*, Am. **27**, 425). Oxidation of sulphocamphylic acid with nitric acid gives sulpho-isopropylsuccinic acid and dimethylmalonic acid (*Koenigs* and *Hörlein*, Ber. **26**, 2044); with permanganate at 0° it is converted into the so-called *dicamphorylic acid* $C_{18}H_{20}O_6$, a diketonic dicarboxylic acid (*Perkin jun.*, J. **75**, 175). The constitution of sulphocamphylic acid is not yet understood (cf. *Bredt*, Ber. **45**, 3821), but α- and β-camphylic acids have been shown to be dehydro-α-campholytic acid (I) and dehydro-β-campholytic acid (dehydro-isolauronolic acid) (II) respectively.



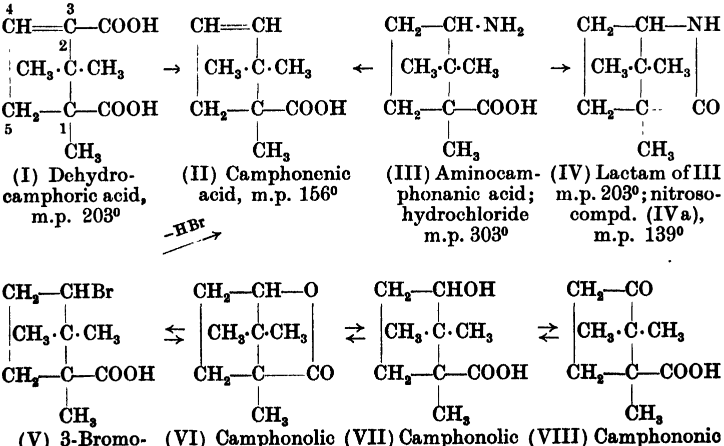
(I)



(II)

The presence of conjugated double bonds in (II) has been proved by the formation of an adduct with α-naphthaquinone (*Lewis* and *Simonsen*, J. **1936**, 734).

Table A. **Camphonane Series.**



(I) Dehydrocamphoric acid, m.p. 203°

(II) Camphonenic acid, m.p. 156°

(III) Aminocamphonanic acid; hydrochloride m.p. 303°

(IV) Lactam of III m.p. 203°; nitroso-compd. (IVa), m.p. 139°

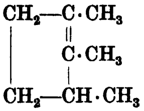
(V) 3-Bromocamphonanic acid, m.p. 147°

(VI) Camphonolic lactone, m.p. 161°

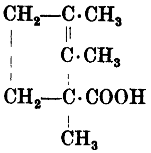
(VII) Camphonolic acid, m.p. (cis) 198°, (trans) 250°

(VIII) Camphononic acid, m.p. 229°

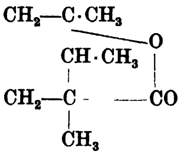
Table B. **Laurolanic Series**



(IX) Laurolene b.p. 121°

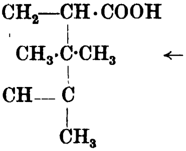


(X) Laurolenic acid b.p. 135°/15 mm

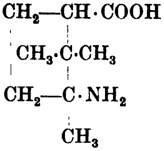


(XI) Laurololactone m.p. 50°, stereoisomeric lactone m.p. 32°

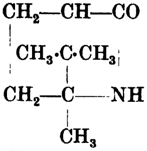
Table C. α-**Campholytic Series** (*Noyes* and *Potter*, Am. **34**, 1068)



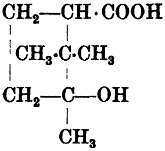
(XII) α-Campholytic acid, b.p. 140°/15 mm. (dehydro-acid = α-camphylic acid)



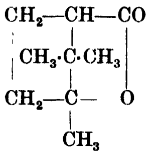
(XIII) Amino-dihydro-α-campholytic acid (hydrochloride, m.p. 261°)



(XIV) Dihydro-α-campholyto-lactam, m.p. 189°; nitroso-compd. m.p. 185°

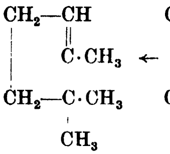


(XV) Hydroxy-dihydro-α-campholytic acid m.p. (trans) 134°, (cis) 118·5°

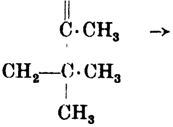


(XVI) Hydroxy-di-hydro-α-campho-lyto-lactone, m.p. 116°

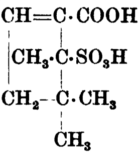
Table D. β- (or **Iso-**) **Campholytic Series**



(XVII) Isocampholytene, b.p. 108°



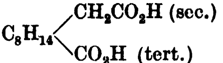
(XVIII) β-Campholytic acid, m.p. 134° (dehydro-acid = β-camphylic acid)



(XIX) Sulpho-camphylic acid (?) m.p. 165°

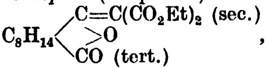
Isocampholytene (*isolaurolene*) (table D, XVII), b.p. 108°, is formed by heating β-campholytic acid to 300°. It has been synthesised by the action of CH_3MgI upon 2:2-dimethylcyclopentanone followed by dehydration of the alcohol formed. Like β-campholytic acid, it is oxidised by $KMnO_4$ to acetylisocaproic acid (pp. 302, 311). It condenses with acetyl chloride in the presence of aluminium chloride to give *1-acetyl-2:3:3-trimethyl-Δ¹-cyclopentene* $C_8H_{13}(COCH_3)$, b.p. 202°, a ketone isomeric with camphor; this ketone is also obtained from the chloride of β-campholytic acid and zinc methyl, and is oxidised by potassium hypobromite to β-campholytic acid (*Blanc*, Bull. **5** (1909), 24).

Laurolene (table B, IX), b.p. 121°, is formed by rearrangement when camphanic acid is heated with water to 180°, and by boiling the nitroso-compound of amino-camphonanic acid lactam (table A, IVa) with caustic soda (*Noyes* and *Derick*, Am. **31**, 669; *Bredt*, J. pr. **83**, 404).

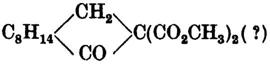


Homocamphoric acid, $C_8H_{14}\left\langle\begin{array}{l}CH_2CO_2H \text{ (sec.)}\\ CO_2H \text{ (tert.)}\end{array}\right.$, m.p. (active) 234°, (*dl*) 232°, is formed by boiling cyanocamphor with aqueous caustic potash; cf.

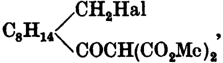
also *Lapworth*, Proc. **16**, 128. Its *mono-nitrile, cyano-campholic acid*, m.p. (active) 164°, is prepared by heating α-campholide with KCN (*Haller*, C. r. **122**, 446; *Komppa*, Ber. **41**, 4470). *Distillation of the Ca salt of homocamphoric acid in a stream of CO_2 yields camphor* (cf. p. 284).

Camphoryl-malonic ester, 

$$C_8H_{14}\left\langle\begin{array}{l}C{=}C(CO_2Et)_2 \text{ (sec.)}\\ \quad >O\\ CO \text{ (tert.)}\end{array}\right.$$

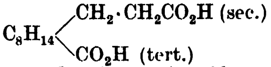
, m.p. 82° (active), b.p. 247°/40 mm., is formed from sodiomalonic ester and camphoric acid chloride (*Winzer*, Ann. **257**, 298). Similar compounds are obtained by interaction of chloro- and bromo-campholic acid chlorides with the sodio-derivative of dimethyl malonate; a halogen-free ester, 

$$C_8H_{14}\left\langle\begin{array}{c}CH_2\\ \\ CO\end{array}\right\rangle C(CO_2CH_3)_2 (\ ?)$$

m.p. 79°, is formed together with two esters containing halogen: 

$$C_8H_{14}\left\langle\begin{array}{l}CH_2Hal\\ \\ COCH(CO_2Me)_2\end{array}\right.$$

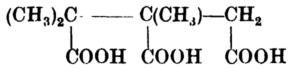
, m.ps. 56° and 73° (*R. Anschutz*, private communication).

Hydrocamphoryl-acetic acid, 

$$C_8H_{14}\left\langle\begin{array}{l}CH_2\cdot CH_2CO_2H \text{ (sec.)}\\ \\ CO_2H \text{ (tert.)}\end{array}\right.$$

, m.p. (active) 142°, is prepared by heating *hydrocamphoryl-malonic acid*, m.p. (active) 178°, obtained by the reduction and hydrolysis of camphoryl-malonic ester (above) (*Winzer*, Ann. **257**, 301).

Camphoronic acid, *ααβ-trimethyl-carballylic acid,*



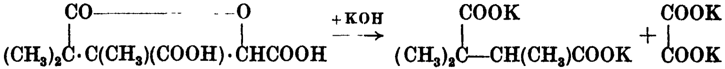
$$\begin{array}{ccc}(CH_3)_2C & \text{——} C(CH_3) & \text{—}CH_2\\ | & | & |\\ COOH & COOH & COOH\end{array}$$

is obtained by the oxidation of camphoric acid (p. 304), camphanic acid, dehydro-camphoric acid, campholic acid, camphonenic acid, etc., with nitric acid. *d*-Camphoric acid gives a laevorotatory, and *l*-camphoric acid gives a dextrorotatory camphoronic acid (*Aschan*, Ann. **302**, 53).

dl-Camphoronic acid has been synthesised in the following way: acetoacetic ester and α-bromisobutyric ester, or better, αα-dimethyl-acetoacetic ester and bromacetic ester, were condensed together in the presence of Zn (*Reformatsky* reaction) to give β-hydroxy-ααβ-trimethylglutaric ester, $ROOC\cdot CH_2C(OH)(CH_3)\cdot C(CH_3)_2COOR$. This with PCl_5 gave the β-chlor-ester, which with KCN yielded the ester of β-cyano-ααβ-trimethylglutaric acid, the mono-nitrile of camphoronic acid. The latter could be hydrolysed to *dl*-camphoronic acid, m.p. 168° (see below) (*Perkin jun.* and *Thorpe*, J. **71**, 1169).

The importance of the decomposition of camphoronic acid into trimethylsuccinic anhydride, isobutyric acid, CO_2, H_2O and carbon for the determination of the constitution of camphor has been mentioned already (p. 284). When rapidly heated, camphoronic acid melts at 156° (active) or 172° (*dl*), and is converted into camphoronic anhydride-acid (*anhydro-camphoronic acid*), b.p. 205°/12 mm., the m.p. of which, 139° (active), 137° (*dl*) is that observed when camphoronic acid is heated slowly. Anhydro-camphoronic acid is converted by PCl_5 into two structurally isomeric *chlorides*, m.ps. (active) 132° and 39°; when distilled in vacuo, the former is converted into the latter. The latter gives with bromine two stereoisomeric *bromo-anhydro-camphoronic acid chlorides*, which are converted by boiling water into the lactones of two unstable hydroxycamphoronic acids; these lactonic dicarboxylic acids are cis- and trans-*camphoranic acids*, and they may be compared to cis- and trans-camphoric acids in the relative position of the two COOH groups.

cis-Camphoranic acid, $C_9H_{12}O_6 + H_2O$, m.p. 209°, *anhydride*, $C_9H_{10}O_5$, m.p. 137°, contains a lactone ring which is very resistant to alkali; fusion with potash gives a good yield of trimethylsuccinic acid and oxalic acid (*Bredt*, Ann. **299**, 131; *Aschan*, Ann. **302**, 51):

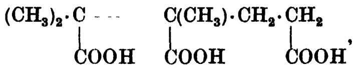


$$\begin{array}{l}CO\text{————}O\\ |\qquad\qquad\qquad\qquad\qquad |\\ (CH_3)_2C\cdot C(CH_3)(COOH)\cdot CHCOOH\end{array} \xrightarrow{+KOH} \begin{array}{l}COOK\qquad\qquad\qquad\quad COOK\\ |\qquad\qquad\qquad\qquad\qquad + |\\ (CH_3)_2C\text{—}CH(CH_3)COOK\quad COOK\end{array}$$

Camphoranic acid   Trimethylsuccinic acid

trans-**Camphoranic acid** ("*β-hydroxy-camphoronic acid*"), m.p. 249°, can be decomposed in the same way. When dehydrated, it yields the anhydride of cis-camphoranic acid (*J. Bredt*, J. pr. **149**, 161).

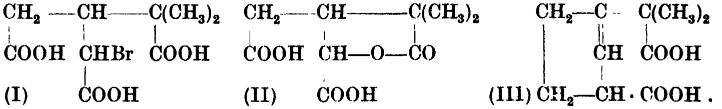
Homocamphoronic acid,



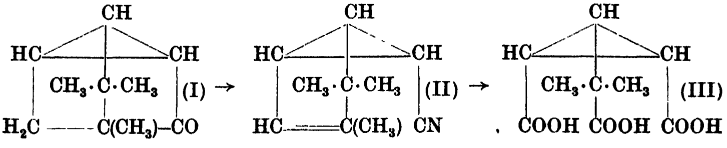
$$\begin{array}{lll}(CH_3)_2\cdot C\text{---} & C(CH_3)\cdot CH_2\cdot & CH_2\\ | & | & |\\ COOH & COOH & COOH\end{array}$$

, m.p. 207° (decomp.), is formed by the action of dilute HNO_3 on αα-dibromocamphor in presence of $AgNO_3$, a profound rearrangement taking place, and by boiling α-bromocampholide with the same reagents for some time (*Kipping*, J. **75**, 137; *Lapworth* and *Chapman*, J. **75**, 995).

Isocamphoronic acid, $HOOC\cdot C(CH_3)_2\cdot CH\cdot(CH_2\cdot COOH)_2$, m.p. 167°, is formed by oxidising α-campholenic acid with $KMnO_4$ (p. 301), dihydroxy-dihydro-campholenic acid being an intermediate. It is also obtained by the oxidation of fenchone and camphenilone (*Nametkin, Grekova* and *Chuchrikova*, C. 1923 I 1500), and of pinonic acid and pinoylformic acid (*Tiemann* and *Semmler*, Ber. **28**, 1348; *Baeyer*, Ber. **29**, 2793); in the two latter cases molecular rearrangement takes place. It has been synthesised by condensing sodio-cyanacetic ester with αα-dimethylglutaconic ester, and hydrolysing the product (*Perkin jun.*, Proc. **16**, 214). When isocamphoronic acid is heated with bromine, the product is **bromo-isocamphoronic acid** (I), which can be used for the preparation of the *lactone*, m p. 256°, of trans-α-**hydroxy-isocamphoronic acid** and the *lactone* (II), m.p. 186°, of cis-α-**hydroxy-isocamphoronic acid** (cf. cis- and trans-camphoranic acids). The latter lactone can also be obtained by oxidation of synthetic **dehydro-camphenic acid** (III) (p. 268) with HNO_3 (*Lipp*, Ber. **47**, 2995):

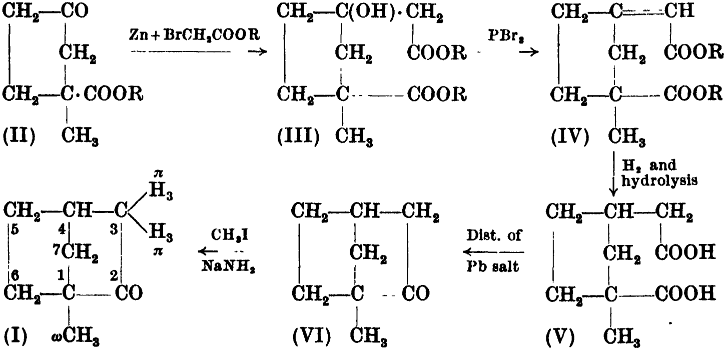


The *oxime* (m.p. 85°) of **3:5-cyclocamphanone** (I) can be dehydrated with ring-fission to give **cyclocampholenic acid nitrile** (II), m.p. 80°, b.p. 111°/17 mm.; this can be hydrolysed with alcoholic potash to **cyclo-campholenic acid** (m.p. 110°), which is oxidised with $KMnO_4$ to **cyclo-isocamphoronic acid** (III), m.p. 230° (*Bredt* and *Holz*, J. pr. **95**, 133). This series of reactions corresponds to the conversion of camphor into isocamphoronic acid (above):



See also the degradation of 4-methyl-camphor to symm. methyl-isocamphoronic acid (*Bredt-Savelsberg* and *Buchkremer*, Ber. **64**, 600), and of 4-phenyl-camphor to symm. phenyl-isocamphoronic acid (id., Ber. **66**, 1921).

Fenchone (I, p. 316), m.p. 6°, b.p. 193°, d_4^{19} 0·9465, n_D^{19} 1·46306, occurs in nature both as the *d*- and the *l*-form; it is very similar to camphor in its properties, but in contrast to that compound it has no technical and only few pharmaceutical uses. *d*-**Fenchone,** $[\alpha]_D$ c. + 65°, was found with camphor in fennel oil by *Wallach* and *Hartmann* in 1890; *l*-**fenchone** was found with pinene, thujone or tanacetone and bornyl esters in thuja oil by *Wallach* in 1892. When heated for some time with nitric acid, fenchone is oxidised mainly to α,α-dimethyl-tricarballylic acid, dimethylmalonic acid and isocamphoronic acid (*Gardner* and *Cockburn*, J. **73**, 708), but dilute nitric acid under pressure gives nitro-derivatives (*Nametkin*, J. pr. **108**, 29). $KMnO_4$ oxidises fenchone to dimethylmalonic, acetic and oxalic acids. Oxidation with CrO_3 gives p-**keto-fenchone,** m.p. 93° (*Bredt*, J. pr. **106**, 344); this can be converted into p-**keto-bromofenchone,** m.p. 132°, and hence into **keto-fencholenic acid,** m.p. 127° (*Bredt* and *Pinten*, J. pr. **119**, 97). Fenchone *oxime* exists in two active geometrically isomeric forms, m.p. 167° and 123° (*W. Hückel* and *Sachs*, Ann. **498**, 179); m.p. (*dl*) 159°; fenchone *isoxime*, m.p. (active) 137°, (*dl*) 161°; fenchone *semicarbazone* is formed with difficulty: m.p. (active) 183°, (*dl*) 172°. On reduction the direction of rotation is inverted, and two stereoisomeric fenchyl alcohols (p. 280) are formed, together with *fenchopinacol*, m.p. 97°. Fenchone rearranges to m-cymene when heated with P_2O_5 (*Richter* and *Wolff*, Ber. **63**, 1724), and with strong sulphuric acid to 1:3:4-acetyl-xylene (*Marsh*, Proc. **15**, 196). Fenchone does not react with sodium bisulphite nor with phenylhydrazine, and does not form a hydroxymethylene compound; with Na and CO_2 two α-hydroxy-acids are formed: α- and β-**fenchocarboxylic acids,** $C_{10}H_{15}O(COOH)$, m.ps. (active) 142°, and 77°; these are converted by dehydration into **anhydro-fenchocarboxylic acid,** m.p. 175°, which seems to have a tricyclic structure (*Wallach*, Ann. **300**, 294). Bromine at 100° converts fenchone into *mono-bromofenchone* $C_{10}H_{15}OBr$, b.p. 131–134°/18 mm. (*Semmler*, Ber. **40**, 434), in which the Br is on the 6- or the ω-carbon atom. The constitutional formula for fenchone (I) was deduced by Semmler from the physical properties of fenchone and from its oxidation products in acid, neutral and alkaline solution (Ch. Ztg. **29**, 1313); it was fully established by the following synthesis carried out by *Ruzicka* (Ber. **50**, 1362). 3-Methylcyclopentanone-3-carboxylic ester (II) undergoes the *Reformatsky* reaction with bromacetic ester and Zn to give (III), which is converted, via (IV) and (V), into **1-methyl-norcamphor** (VI); this was twice methylated in the 3-position to give fenchone (I):



For the synthesis of fenchone from camphenic acid, via camphenonic acid, see p. 298.

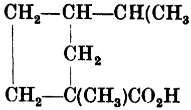
Fenchone is oxidised in the animal organism to 4-hydroxy-, 5-hydroxy- and π-hydroxy-fenchone (*Reinartz* and *Zanke*, Ber. **69**, 2259).

Fenchone has been recommended as a substitute for camphor in the treatment of rheumatism ("*terpacid*") (C. 1921 IV 486).

Thiofenchone, $C_{10}H_{16}S$, has m.p. 24°, b.p. 208°/24 mm. (*Rimini*, Gazz. **39** II 209).

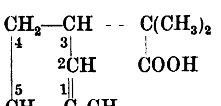
Fenchone undergoes a ring fission when heated to 230° with caustic potash, or when treated with sodamide, a reaction which is similar to the conversion of camphor into campholic acid (p. 303) and camphenilone into dihydro-camphoceenic acid (p. 319); the product is

Fencholic acid, *1-methyl-3-isopropylcyclopentane-1-carboxylic acid*

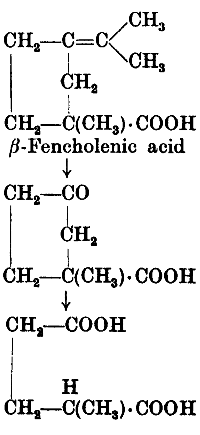


m.p. 19°, b.p. 152°/17 mm.; this has been synthesised (*Bouveault* and *Levallois*, C. r. **148**, 1524). The *chloride* has b.p. 100°/15 mm.; the *amide* has m.p. (active) 94°, (*dl*) 116° (*Wallach*, Ann. **369**, 71). The Hofmann degradation of this amide gives fenchelyl isocyanate, $C_9H_{17}N{:}CO$, and then *fenchelylamine*, $C_9H_{17}NH_2$, b.p. 173° (*Wallach*, Ann. **369**, 79; *Bouveault* and *Levallois*, Bull. **7** (1910), 683; *v. Braun*, Ann. **490**, 126; *v. Braun* and *Friehmelt*, Ber. **66**, 684; *v. Braun* and *Jacob*, Ber. **66**, 1461). **α-Fencholenic acid,** $C_9H_{15}COOH$, a liquid, b.p. 255°, and **β-fencholenic acid,** m.p. 73°, b.p. 260°, are obtained by the hydrolysis of their *nitriles*: α-, b.p. 212°, β-, b.p. 218°, which are formed both together by boiling fenchone oxime with dilute sulphuric acid (*Cockburn*, J. **75**, 501). β-Fencholenic nitrile is hydrolysed more readily to the acid than α-fencholenic nitrile, which is converted first into the *amide*, m.p. (active) 114°, (*dl*) 99°, so that the two acids can easily be separated by this method. The formulae for the two acids show that the decomposition of fenchone oxime is not so simple as that of camphor oxime.

Several important derivatives of α-fencholenic acid are known. **α-Fencholene-amine** (I), b.p. 205°, is formed by the reduction of α-fencholenic nitrile (*Wallach*, Ann. **300**, 310); **α-fencholene-alcohol,** b.p. 218°, can be prepared from α-fencholenic amide (*id.*, *ib.* **284**, 337), and gives the ether, **fenchenol** (II), b.p. 183°, when heated with dilute acids. β-Fencholenic acid is degraded by ozone to **3-methylcyclopentanone-3-carboxylic acid** (III), m.p. 170°, *semicarbazone* m.p. 199° (cf. the synthesis of fenchone); further oxidation gives a tricarboxylic acid, and finally α-methylglutaric acid (IV), m.p. 78°, Both α- and β-fencholenic acids are converted into lactones by conc. sulphuric acid; the α-acid gives the *lactone* of *hydroxy-dihydro-α-fencholenic acid* $C_{10}H_{18}O_2$, m.p. 78°, and the β-acid the *lactone* of *hydroxydihydro-β-fencholenic acid*, m.p. 69° (*Semmler*, Ber. **39**, 2853); the latter is found among the oxidation products of fenchyl alcohol (p. 280). A third isomeric acid, $C_9H_{15}COOH$, **γ-fencholenic acid,** b.p. 146°/10 mm., easily converted into α-fencholenic acid, is formed by the action of hot alcoholic potash upon bromofenchone; on ozonisation cyclobutane-2-[α-isobutyric acid], *semicarbazone* m.p. 192°, is formed (*ib. id.* **40**, 432).



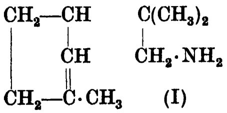
α-Fencholenic acid (or $\Delta^{5(1)}$-)

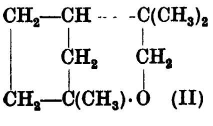


β-Fencholenic acid

(III)

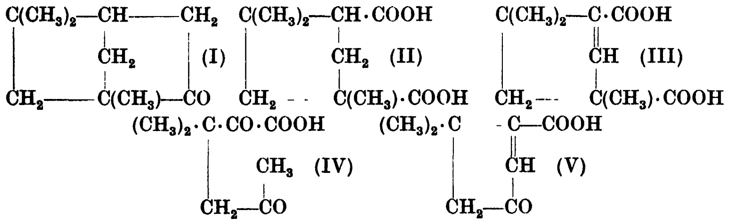
(IV)





Fenchone and CH_3MgI give tert.-**methylfenchol,** $C_9H_{16}>C\langle^{OH}_{CH_3}$, m.p. 61°, b.p. 87°/10 mm., which has a peculiar sweetish mouldy smell. When it is dehydrated, the main product is 1-methylcamphene, which is converted by the Bertram-Walbaum method to 4-methyl-isoborneol; for the mechanism of this reaction, see p. 267. Since this 1-methylcamphene is also the chief product of the dehydration of tert.-methyl-borneol, and can be converted into fenchone by ozonisation, it is clear that camphor can be converted into fenchone via tert.-methylborneol and 1-methylcamphene.

Isofenchone, $C_{10}H_{16}O$ (I), b.p. 201°, is prepared by the oxidation of isofenchyl alcohol with chromic acid (p. 280); *oxime,* m.p. (active) 82°, (*dl*) 133°; *semicarbazone,* m.p. (active) 221–222°, (*dl*) 223–224°; *hydrazone,* m.p. 111–112°; with bromine it gives *monobromo-isofenchone,* m.p. (active) 57°, (*dl*) 47°. When heated with caustic potash, it is decomposed into **isofencholic acid,** $C_{10}H_{18}O_2$, m.p. 34°; *amide* m.p. 66°. Oxidation with $KMnO_4$ yields a dicarboxylic acid, **isofenchocamphoric acid,** $C_{10}H_{16}O_4$ (II), which, like camphoric acid, is a ring-substituted glutaric acid and has two asymmetric carbon atoms; all the four optically active forms and both racemates are known: cis-(active) m.p. 159°, $[\alpha]_D \pm 14{\cdot}54°$ (in ethyl alcohol); (*dl*) m.p. 173°; trans-(active) m.p. 150°, $[\alpha]_D \pm 4{\cdot}16°$ (in ethyl alcohol); (*dl*) m.p. 174°. Isofenchocamphoric *anhydride* has m.p. (active) 98°, (*dl*) 96° (*Sandelin,* Ann. **396,** 299). Camphoric acid can be converted into dehydro-camphoric acid, and similarly isofenchocamphoric acid gives **dehydro-isofenchocamphoric acid** (III), m.p. (active) 171°, (*dl*) 191°; because of the meso-trans-position of the carboxyl groups this cannot form a monomolecular anhydride (cf. dehydro-camphoric acid; and *Bredt,* Ann. **437,** 10).



Alkaline permanganate oxidises (III) to $\alpha\delta$-**diketo-**$\beta\beta$**-dimethylcaproic acid** (IV), which in the presence of alkali undergoes ring-closure to give **4:4-dimethyl-**Δ^2**-cyclopentenone-3-carboxylic acid** (V) (*Toivonen,* Ann. **419,** 184).

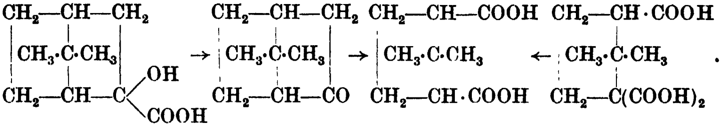
Isofenchone and CH_3MgI yield tert.-**methyl-isofenchol,** m.p. 47°; dehydration of this compound gives the ring-unsaturated *2-methyl-isofenchene* (*methyl-isofenchylene*), $C_{11}H_{18}$, b.p. 160–162°, which can be oxidised to *dl,* cis-isofenchocamphoric acid. 1-Methyl-β-fenchene is also obtained in the oxidation and can be reconverted into isofenchone (*Komppa,* Ann. **472,** 179; **523,** 87).

4-Methylsantenone: see *Toivonen,* C. 1935 II 2959, and *Komppa* and *Nyman,* Ber. **69,** 712.

The following lower homologues of camphor and fenchone will now be dealt with: **apocamphor, santenone** = π-**apocamphor,** and **camphenilone,** all of the constitution $C_9H_{14}O$, **1-methyl-norcamphor** and **3-methyl-norcamphor,** $C_8H_{12}O$, and **norcamphor,** $C_7H_{10}O$. With the exception of π-apocamphor, they differ from camphor and fenchone in that they do not occur in nature and have been obtained only by synthesis.

Apocamphor, α-*fenchocamphorone* (I), m.p. (active and *dl*) 110°, b.p. 202°, is formed by the ozonisation of α-fenchene (p. 272), and by the further oxidation of hydroxy-α-fenchenic acid (II), m.p. 153° (*Komppa* and *Roschier,* Ann. **470,** 129); it can be obtained from the Pb salt of homo-apocamphoric acid by dry distillation (cf. camphor) (*Komppa,* Ber. **47,** 934). **Apoborneol** has m.p. (active) 130°, (*dl*) 124°. The oxidation of apocamphor yields **apo-**

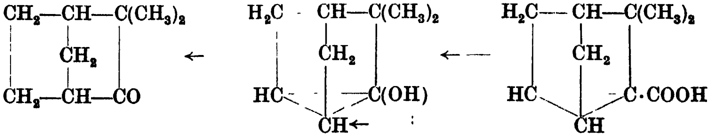
camphoric acid ("*camphopyric acid*") (III), m.p. (cis) 204°, (trans) 190°; this can also be obtained by loss of CO_2 from **carboxy-apocamphoric acid** (IV), an oxidation product of ketopinic acid (p. 297) and of camphene (*Jagelki*, Ber. **32**, 1498). Apocamphoric acid can be obtained synthetically from diketo-apocamphoric acid (p. 69) by a series of reductions (*Komppa*, Ann. **368**, 126). In agreement with its symmetrical structure the cis-form of apocamphoric acid is inactive (meso-form; see *Bredt*, Ch. Ztg. **20**, 840); in other respects the acid behaves like camphoric acid. **Chloro-apocamphoric acid,** m.p. 171°, yields **hydroxy-apocamphoric acid,** m.p. 197°, and **apocamphanic acid,** m.p. 167°, when treated with alkali (*J. Bredt*, private communication).



(II) (I) (III) (IV)

Dehydro-apocamphoric acid, m.p. 224°, and **isodehydro-apocamphoric** acid, m.p. 209° (*Komppa*, Ann. **368**, 149), and **apocampholide,** m.p. 164° (*id.*, Ber. **47**, 936) are prepared in the same way as the corresponding derivatives of camphor, and resemble them closely in their properties.

Camphenilone (I) is related to fenchone in the same way as apocamphor to camphor; m.p. (active) 37–38·5°, (*dl*) 39°, b.p. 192°; cryoscopic constant 605 (*Dulou*, Bull. Pin (2) **1934**, 210). It is easily accessible from camphene (p. 268). *Semicarbazone*, m.p. (active and *dl*) 224°. Camphenilone has been synthesised by the methylation of norcamphor, and by the degradation of isocamphenilanic acid (*G. Komppa* and *O. Komppa*, Ber. **69**, 2606). Dehydration of either of the two isomeric *oximes* of camphenilone (m.ps. 110° and 165°) yields the nitrile of α-camphoceenic acid, which can be hydrolysed to *α-camphoceenic acid* (p. 303; cf. α-fencholenic and α-campholenic acids). The final degradation product of camphenilone is dimethyl-tricarballylic acid. **Dihydro-camphoceenic acid,** b.p. 139°/12 mm., corresponds to fencholic acid; its *amide*, m.p. 168°, is formed by the action of sodamide upon camphenilone (*Semmler*, Ber. **39**, 2580). CrO_3 oxidises camphenilone to **p-keto-camphenilone,** m.p. (active) 74°, (*dl*) 56° (*Bredt* and *Pinten*, J. pr. **119**, 91). **Camphenilol,** the reduction product of camphenilone, exists in two stereoisomeric forms (cf. p. 276), m.p. (active) 76° and 98–101° (*W. Huckel* and *Tappe*, Ber. **69**, 2769); it can be converted into *camphenilyl chloride* m.p. 50°, and thence into santene (p. 271). The dehydration of camphenilol gives apocyclene and santene (*Komppa* and *Nyman*, Ber. **69**, 334). Camphenilone is also formed by the intramolecular rearrangement of **apotricyclol** (II), b.p. 82–86°/12·5 mm., m.p. 75–80° (indef.), which may therefore be considered as a kind of cyclic enol form of camphenilone. Apotricyclol is obtained from **tricyclenic acid** (III), $C_{10}H_{14}O_2$, m.p. 150°, by way of the *amide*, m.p. 118°, and apotricyclylamine (*Lipp* and *Padberg*, Ber. **54**, 1316).

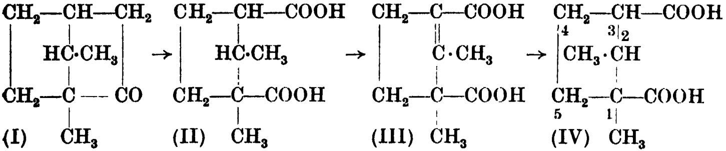


(I) (II) (III) (see also p. 275)

Tricyclol, $C_{10}H_{16}O$, m.p. 112°, which is prepared by the reduction of the methyl ester of tricyclenic acid, can be oxidised to the aldehyde **tricyclal,** $C_{10}H_{14}O$, m.p. 90°, *semicarbazone* m.p. 220°. The decomposition of the hydrazone of tricyclal gives tricylene (p. 275), a fact of great importance in the determination of the structure of this hydrocarbon (*Lipp*, Ber. **58**, 772; cf. also *Komppa*, Ber. **62**, 1366).

For **β-fenchocamphorone,** the lower homologue of isofenchone, see under β-fenchene (p. 272); for an attempt to synthesise it, see *Bardhan, Banerji* and *Bose* (J. **1935,** 1127).

Santenone, *π-apocamphor* (I), is found in a weakly laevorotatory form in East Indian sandalwood oil. The *dl*-form, m.p. 50°, *semicarbazone* m.p. 229°, is formed by the oxidation of α-santenol obtained from santene and by the dry distillation of the Ca salt of homosantenic acid (*Enkvist,* J. pr. **137,** 275). Santenone is very similar to camphor, and a great number of its reactions are analogous to those of camphor. Corresponding to isoborneol and borneol, we have **α-santenol,** *π-apo-isoborneol,* and **santene alcohol,** *π-apoborneol* (obtained from the former by the action of sodium ethoxide); similarly we have **isonitroso-santenone, santenone quinone, cyanosantenone, santenone-carboxylic acid,** etc. For the products from santenone in the *Grignard* reaction, see *Komppa* and *Nyman,* Ann. **517,** 105; Ber. **69,** 712. Santenol, santene-alcohol and santenone give by oxidation **santenic acid,** $C_9H_{14}O_4$ (II), which is known in cis- and trans-forms. It can be converted via **bromosantenic acid** and **santenenic acid** (III) into **cis-allosantenic acid** (IV); the constitution of this has been proved by its synthesis from oxalic ester and β-methylglutaric ester, a series of reactions analogous to Komppa's synthesis of camphoric acid. The isomerism of these acids depends on the different positions taken up by the methyl group on C_2, as shown in the formulae II and IV (*Enkvist,* J. pr. **137,** 261; *Komppa* and *Rohrmann,* Ber. **67,** 828). For a synthesis, see *Komppa* and *Rohrmann,* Ann. Acad. Sci. fenn. **44,** No. 3, 3 (1936).



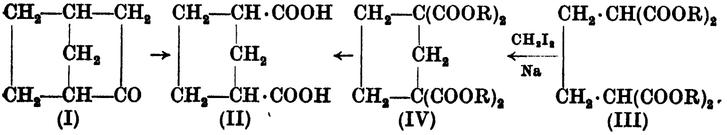
cis-Form m.p. 171°
Anhydride m.p. 116°
trans-Form m.p. 167°

cis-Form m.p. 152°
Anhydride m.p. 92·5°
trans-Form m.p. 130°

1-Methyl-norcamphor is an intermediate in Ruzicka's synthesis of fenchone (p. 316, formula VI); *semicarbazone,* m.p. 210–211°.

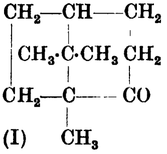
3-Methyl-norcamphor, apo-camphenilone (p. 186) is prepared by a diene synthesis, and by distillation of the Pb salt of methyl-homonorcamphoric acid; the latter is the oxidation product of 5-methyl-[1:2:3]-bicyclo-octan-7-ol, which is obtained from santene-diketone (p. 194) (*Komppa,* Ber. **86,** 1127; *Komppa* and *Beckmann,* Ann. **523,** 68).

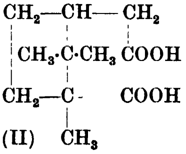
Norcamphor (I), m.p. 94°, *semicarbazone* m.p. 197°, is prepared synthetically from homo-norcamphoric acid in the same way as camphor is prepared from homocamphoric acid (*Hintikka* and *Komppa,* C. 1918 II 369). It can also be obtained by a diene synthesis, from the condensation product of cyclopentadiene and acrolein (p. 22). Its oxidation product, **norcamphoric acid** (II) (cyclopentane-1:3-dicarboxylic acid), m.p. (cis) 121°, (trans) 88°, *anhydride* m.p. 161°, was the first ring-substituted glutaric acid to be synthesised; *Wislicenus* and *Pospischill* prepared it by condensing the Na-compound of the tetracarboxylic ester (III) with methylene iodide, followed by hydrolysis and decarboxylation of the product (IV) (*Pospischill,* Ber. **31,** 1953) (see also p. 63):

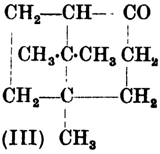


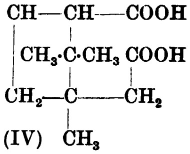
Norborneol exists in two diastereoisomeric forms (see p. 276): *dl, β*-norborneol (exo-form), m.p. 126–127°, *phenylurethane* m.p. 144–145°; *dl, α*-norborneol (endo-form), m.p. 149°, *phenylurethane* m.p. 159–160° (*Alder* and *Stein*, Ann. **525**, 201). **Norcamphane,** m.p. 86–87°, the fundamental hydrocarbon with a bicyclic ring-system composed of a six-membered ring with a para-methylene bridge, is prepared from norbornylamine (p. 273).

Ring-homologues of camphor and its derivatives with 8 carbon atoms in the ring-system can be prepared by the distillation of the Ca or Pb salts of the homologous camphoric acids; they are derivatives of [*1*:*2*:*3*]-*bicyclo-octane* (see p. 194). *Winzer's* hydro-camphoryl-acetic acid yields **homocamphor** (I), $C_{11}H_{18}O$, m.p. 190°, *semicarbazone* m.p. 252°, *oxime* m. p. 168°, which can be converted via the isonitroso-compound into **homocamphoric acid** (II) (*Lapworth* and *Royle*, J. **117**, 793); cf. the synthesis of camphor, p. 284. **Homo-epicamphor** (III), m.p. 204°, *semicarbazone* m.p. 245°, *oxime* m.p. 105°, is formed in a similar way from α-carboxycamphocean-β-propionic acid, 1:2:2-trimethylcyclopentane-1-propionic-3-carboxylic acid (*Salmon-Legagneur*, C. r. **192**, 748); isonitroso-homo-epicamphor can be converted into **β-homocamphoric acid** (IV), m.p. 222° (cf. isonitroso-homocamphor, above). The constitution of the latter is established by the formation of epicamphor in the distillation of its Pb salt (*Salmon-Legagneur*, C. r. **194**, 467; Bull. **51** (1932), 807).


(I)


(II)


(III)


(IV)

For R-**homocamphenilone** and **carbocamphenilonone,** see under camphene, p. 269, and *Hintikka*, Ber. **47**, 512; C. 1919 I 840; for **carbofenchonone,** the higher homologue of carbocamphenilonone, see *Wallach* and *Westphalen*, Ann. **315**, 275. The oxidation product of santene glycol yields **5-methyl-[1:2:3]-bicyclo-octen-7-one** (*Semmler* and *Bartelt*, Ber. **41**, 871; p. 194); the same type of ring-system is present in **[1:2:3]-bicyclo-octan-2-one,** which is obtained by the distillation of the Ca salt of hexahydrohomo-isophthalic acid (*Komppa* and *Hirn*, Ber. **36**, 3610).

D. THE SESQUITERPENES AND THE POLYTERPENES

The sesquiterpenes have the composition $C_{15}H_{24}$, and are widely distributed in essential oils. A large number of sesquiterpenes have been isolated as individuals, but many of these appear to be identical. They are faintly-coloured, rather viscous oils, with a slight and not very pleasant smell; they boil between 250° and 280°, and some resinify very readily. On the basis of their chemical and physical properties, particularly their molecular refraction and specific gravity, they are placed in four groups (*Semmler*, Konstitution der Sesquiterpene und Sesquiterpenalkohole, Breslau 1910):

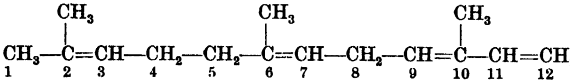
1. Acyclic sesquiterpenes with 4 double bonds
   ($[R_l]_D$ 69·60; $d \sim$ 0·84);
2. Monocyclic sesquiterpenes with 3 double bonds
   ($[R_l]_D$ 67·87; $d \sim$ 0·87–0·89);
3. Bicyclic sesquiterpenes with 2 double bonds
   ($[R_l]_D$ 66·13; $d \sim$ 0·90–0·92);
4. Tricyclic sesquiterpenes with 1 double bond
   ($[R_l]_D$ 64·40; $d \sim$ 0·91–0·935).

Fully saturated sesquiterpenes are unknown. The relationship existing between isoprene, C_5H_8, and the terpenes, $C_{10}H_{16}$, a relationship which is not merely a matter of formulae, exists also between isoprene and the sesquiterpenes (see p. 197); the hypothesis that the sesquiterpenes should be formulated as the condensation products of three isoprene molecules has been of great value in the determination of the structures of a number of these hydrocarbons (see *Ruzicka*, Über Konstitution und Zusammenhänge in der Sesquiterpenreihe, Berlin 1928). Three molecules of isoprene can be condensed together in various ways; *inter alia* they can give a substituted hydrogenated naphthalene ring, or a system which is easily converted into such a compound. A large number of sesquiterpenes have been dehydrogenated with sulphur and selenium, and some of them have yielded naphthalene derivatives; hence these are hydrogenated naphthalene derivatives or compounds which can readily be transformed into hydrogenated naphthalene derivatives. Other cyclic sesquiterpenes, however, yield no characteristic dehydrogenation products, and probably contain a more complex ring system, e.g. with a bridged ring. These indications have lead to a further division of the three groups of cyclic sesquiterpenes (*Ruzicka*, see below). Besides the dehydrogenation of the sesquiterpenes, the addition of hydrogen halides, NOCl, N_2O_3 and N_2O_4 is used for their characterisation and separation, well-crystalline derivatives often being obtained.

Like the true terpenes, the sesquiterpenes give oxygen derivatives, e.g. $C_{15}H_{24}O$ and $C_{15}H_{26}O$, the *sesquiterpene alcohols* or "*sesquicamphors*", which in contrast to the hydrocarbons usually crystallise well. A few sesquiterpene ketones are also known.

1. Acyclic Sesquiterpenes. — (a) Hydrocarbons $C_{15}H_{24}$.

Sesquicitronellene, b.p. 140°/9 mm., d^{20} 0·8489; n_D 1.53252, occurs in Java citronella oil. On hydrogenation with Pt and H_2 8 H-atoms are taken up and the octahydride, $C_{15}H_{32}$, is formed, but with Na and alcohol only 2 H-atoms enter the molecule (*Semmler* and *Spornitz*, Ber. **46**, 4025). Very similar to sesquicitronellene is **farnesene,** b.p. 128–130°/12 mm., d_4^{18} 0·8385, n_D^{18} 1·4965, which is obtained by the dehydration of nerolidol and of farnesol with acetic anhydride (*Ruzicka*, Helv. **6**, 492); it is probably a mixture of hydrocarbons. The following compound is called α-farnesene



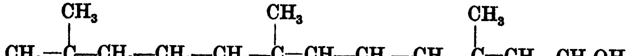
$$\underset{1}{CH_3}—\underset{2}{\overset{\overset{CH_3}{|}}{C}}=\underset{3}{CH}—\underset{4}{CH_2}—\underset{5}{CH_2}—\underset{6}{\overset{\overset{CH_3}{|}}{C}}=\underset{7}{CH}—\underset{8}{CH_2}—\underset{9}{CH}=\underset{10}{\overset{\overset{CH_3}{|}}{C}}—\underset{11}{CH}=\underset{12}{CH_2}$$

(*Terpinolene form*)

Since farnesol (see below) is a mixture of limonene and terpinolene forms (*Ruzicka*, Helv. **6**, 495), farnesene must also contain both forms. A further possibility of isomerism is given by the fact that the double bond can be $\Delta^{9\cdot10}$, as in α-farnesene, or can link C-atom 10 to the side-chain methyl group, as in β-farnesene. Both of these acylic sesquiterpenes are converted into monocyclic sesquiterpenes when heated with conc. formic acid (cf. the conversion of dihydromyrcene into cyclo-dihydromyrcene, p. 200); see bisabolene, p. 324.

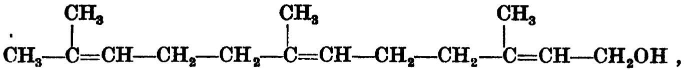
(b) The **Alcohols** $C_{15}H_{26}O$ contain three double bonds and are mixtures of the limonene and terpinolene forms.

Farnesol,



$$CH_2=\overset{\overset{CH_3}{|}}{C}—CH_2—CH_2—CH_2—\overset{\overset{CH_3}{|}}{C}=CH—CH_2—CH_2—\overset{\overset{CH_3}{|}}{C}=CH—CH_2OH$$

(*Limonene form*)

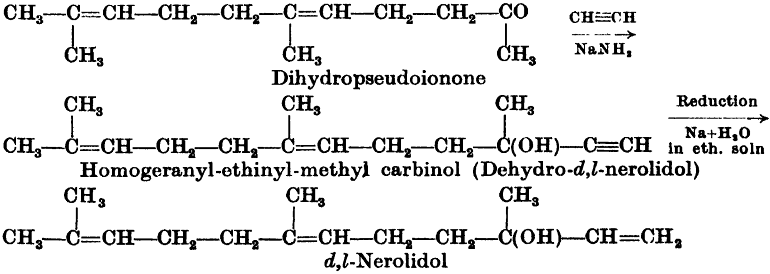


$$\mathrm{CH_3{-}\overset{CH_3}{\overset{|}{C}}{=}CH{-}CH_2{-}CH_2{-}\overset{CH_3}{\overset{|}{C}}{=}CH{-}CH_2{-}CH_2{-}\overset{CH_3}{\overset{|}{C}}{=}CH{-}CH_2OH}\ ,$$

(*Terpinolene form*)

b.p. 120°/0·2 mm.; d^{18} 0·885–0·895; n_D 1·488–1·492, occurs in many strongly-scented essential oils, such as ambrette-seed oil, and particularly in the oils from flowers, e.g. from lime, cyclamen, etc. (*Elze*, C. 1928 II 499). In high dilution it has a scent like that of the lily of the valley. Farnesol is the geraniol of the sesquiterpene series; CrO_3 oxidises it to the aldehyde **farnesal** $C_{15}H_{24}O$, b.p. 173–174°/14 mm., *semicarbazone* m.p. 135°. The corresponding acid, **farnesenic acid** $C_{15}H_{24}O_2$, b.p. 202–206°/16 mm., is obtained via the nitrile from farnesal oxime; *dihydro-pseudo-ionone* $C_{13}H_{22}O$, is also formed by loss of two C-atoms (*Kerschbaum*, Ber. **46**, 1735). Farnesyl bromide has been used for the synthesis of squalene $C_{30}H_{50}$ (*Karrer* and *Helfenstein*, Helv. **14**, 78). Farnesol can be prepared from nerolidol (see below) by treatment with acetic anhydride and hydrolysis of the resulting acetate (*Ruzicka*, Helv. **6**, 483); farnesene is also formed (see above). Farnesol gives a tri-ozonide which can be decomposed into acetone (from the terpinolene form), laevulinic aldehyde, glycollic aldehyde and formaldehyde (from the limonene form). Besides this structural (double-bond) isomerism, the occurrence of which is also shown by the degradation products, cis-trans-isomerism is also possible; these facts explain the variations observed in the physical properties. Catalytic reduction of farnesyl acetate, followed by hydrolysis, yields **hexahydro-farnesol,** $C_{15}H_{32}O$, b.p. 151–152·5°/10 mm., which can be converted into *hexahydro-farnesyl bromide,* $C_{15}H_{31}Br$, b.p. 150–154°/10 mm.; this has been used to build up the ketone **2:6:10-trimethyl-pentadecan-14-one,** $C_{18}H_{36}O$, b.p. 173·5–174°/10 mm., *semicarbazone* m.p. 66–67°, which is identical with the product obtained from *phytol*, $C_{20}H_{40}O$, (I, 152) by oxidation with chromic acid or ozonolysis (*Fischer* and *Lowenberg*, Ann. **475**, 183).

Nerolidol, b.p. 97°/0·2 mm.; d^{15} 0·880; n_D^{20} 1·480, $[\alpha]_D + 12{\cdot}48°$; *phenyl-urethane* m.p. (active) 37°, is the linalool of the sesquiterpene series; it is found in balsam of Peru and in oil of neroli (oil of orange blossom), and has a strong, pleasant smell. Just as linalool gives citral, nerolidol gives farnesal on oxidation with CrO_3; heating with acetic anhydride yields farnesyl acetate and farnesene. The formula of nerolidol has been confirmed by synthesis (*Ruzicka*, Helv. **6**, 492): geranyl chloride is condensed with sodio-acetoacetic ester, and the product subjected to ketonic hydrolysis; the resulting dihydro-pseudo-ionone is treated according to the following scheme:



$$\mathrm{CH_3{-}\underset{CH_3}{\underset{|}{C}}{=}CH{-}CH_2{-}CH_2{-}\underset{CH_3}{\underset{|}{C}}{=}CH{-}CH_2{-}CH_2{-}\underset{CH_3}{\underset{|}{CO}}}\ \xrightarrow[\mathrm{NaNH_2}]{\mathrm{CH\equiv CH}}$$

Dihydropseudoionone

$$\mathrm{CH_3{-}\overset{CH_3}{\overset{|}{C}}{=}CH{-}CH_2{-}CH_2{-}\overset{CH_3}{\overset{|}{C}}{=}CH{-}CH_2{-}CH_2{-}\overset{CH_3}{\overset{|}{C}}(OH){-}C{\equiv}CH}\ \xrightarrow[\text{Na+H}_2\text{O in eth. soln.}]{\text{Reduction}}$$

Homogeranyl-ethinyl-methyl carbinol (Dehydro-*d,l*-nerolidol)

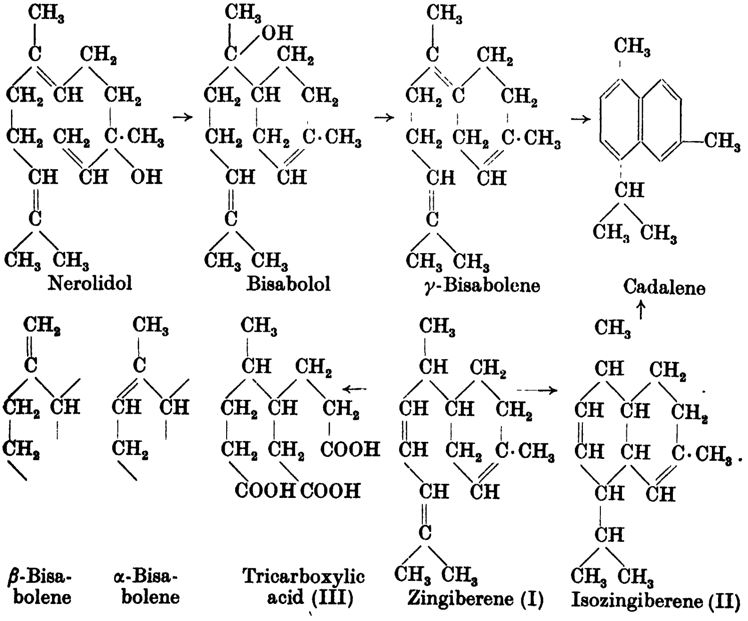
$$\mathrm{CH_3{-}\overset{CH_3}{\overset{|}{C}}{=}CH{-}CH_2{-}CH_2{-}\overset{CH_3}{\overset{|}{C}}{=}CH{-}CH_2{-}CH_2{-}\overset{CH_3}{\overset{|}{C}}(OH){-}CH{=}CH_2}$$

d,l-Nerolidol

Since it has been synthesised from geraniol, which is a mixture of terpinolene and limonene forms, and since it is related to farnesol, nerolidol must also be a mixture of the two forms. As nerolidol can be converted into farnesol, this synthesis is also a synthesis of the latter. The cyclisation of farnesol and nerolidol gives bisabolol (p. 324).

2. Monocyclic Sesquiterpenes. As stated on p. 322, the cyclic sesquiterpenes can be divided into two groups, according as they yield or do not yield the naphthalene derivatives, cadalene and eudalene (see below), when dehydrogenated with S or Se. Bisabolene and zingiberene belong to the "cadalene type", while the synthetic cyclo-isoprene-myrcene and the alcohol elemol belong to the "eudalene type". The curcumenes do not give naphthalene derivatives.

(a) **Hydrocarbons** $C_{15}H_{24}$. — **Bisabolene,** *limene,* is after cadinene and caryophyllene, the most widely distributed sesquiterpene hydrocarbon which occurs naturally; it is present in Bisabol myrrh, oil of lime (*Citrus limetta*), oil of opopanax, bergamot oil, citronella oil, camphor oil, Siberian pine needle oil, etc. The natural hydrocarbon and that regenerated from the *trihydrochloride,* m.p. 79·5°, can theoretically be a mixture of three isomers, α, β and γ (see below), which differ in the position of one double bond; these three isomers give the same trihydrochloride, *trihydrobromide,* m.p. 84°, and hexahydro-derivative (*Semmler* and *Rosenberg,* Ber. 46, 769). With bromine, however, three *hexabromides* are obtained, m.ps. 154°, 142°, and 132° (*Asahina* and *Tsukamoto,* J. Pharm. Soc. Japan **1926,** No. 538, 97). Bisabolene regenerated from its trihydrochloride has b.p. 267°/757 mm.; d^{15} 0·8748; $\alpha_D \pm 0$; n_D^{20} 1·49063. When ozonised, it yields acetone, laevulinic acid and some succinic acid; the ozonisation of tetrahydro-bisabolene gives 2-methylheptan-6-one and 4-methylcyclohexanone; from these fragments, which are also obtained from natural bisabolene, it follows that the γ-form is the chief constituent of these bisabolenes (*Ruzicka* and *van Veen,* Ann. **468,** 133). Exactly as linalool can be cyclised to α-terpineol (p. 223), nerolidol gives a monocyclic tertiary alcohol with two double bonds, **bisabolol,** which is converted by HCl into bisabolene trihydrochloride. This gives a synthetic bisabolene identical with natural bisabolene (*Ruzicka* and *Capato,* Helv. 8, 259). For the synthesis of bisabolol from 1-methyl-4-acetyl-Δ^1-cyclohexene and 2-methyl-5-bromo-Δ^2-pentene, see *Ruzicka* and *Liguori,* Helv. **15,** 3. The energetic treatment of nerolidol or bisabolene with conc. formic acid gives a bicyclic hydrocarbon, a hexahydrocadalene which readily yields cadalene on dehydrogenation:



Nerolidol → Bisabolol → γ-Bisabolene → Cadalene

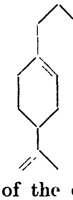
β-Bisabolene α-Bisabolene Tricarboxylic acid (III) ← Zingiberene (I) → Isozingiberene (II) → Cadalene

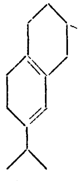
Zingiberene (I), b.p. 129°/9 mm.; d^{20} 0·8684; n_D 1·4956; $[\alpha]_D$ — 73°38′, occurs together with bisabolene in oil of ginger (*Ruzicka* and *van Veen*, Ann. **468**, 143); *nitrosochloride* m.p. 97°. Catalytic hydrogenation gives a hexahydride $C_{15}H_{30}$ (*Semmler* and *Becker*, Ber. **46**, 1814), while sodium and alcohol give only dihydro-zingiberene; from this it can be concluded that conjugated double bonds are present in the side-chain. This dihydro-zingiberene is degraded by $KMnO_4$ to a keto-dicarboxylic acid, $C_{12}H_{20}O_5$, which with NaOBr gives a tricarboxylic acid $C_{11}H_{18}O_6$ (III); the formula of zingiberene is based upon these results. The *dihydrochloride* $C_{15}H_{26}Cl_2$, m.p. 170°, prepared from zingiberene and HCl, and the *dihydrobromide*, m.p. 176°, obtained in the same way, are derivatives of a bicyclic isomerisation product of zingiberene, **isozingiberene** (II), b.p. 120–123°/8 mm., d^{20} 0·9150, n_D 1·5034, $[\alpha]_D$ — 41°. This hydrocarbon is obtained from the hydrogen halides by removal of HCl or HBr, and also by the action of acetic-sulphuric acids in the cold upon zingiberene itself. Catalytic hydrogenation shows that it contains only two double bonds, and dehydrogenation with sulphur gives cadalene. This isomerisation to isozingiberene is the cause of the formation of cadalene in the dehydrogenation of zingiberene itself (*Ruzicka*, *Meyer* and *Mingazzini*, Helv. **5**, 345).

α- and **β-Curcumene** are obtained from the oil present in the rhizomes of *Curcuma aromatica*; α-curcumene, b.p. 128–130°/9 mm., is very stable; its *nitrol-benzylamine* has m.p. 102–104°. β-Curcumene, b.p. 128–130°/6 mm., on the other hand, undergoes isomeric change when heated; its *trihydrochloride* has m.p. 84–85°. Both hydrocarbons are laevorotatory; they are monocyclic and contain three double bonds, and give no derivatives of naphthalene on dehydrogenation (*Rao* and *Simonsen*, J. **1928**, 2496).

Cyclo-isoprene-myrcene, b.p. 242–244° (*trihydrochloride* m.p. 81°), obtained by heating together myrcene and isoprene (*Semmler* and *Jonas*, Ber. **47**, 2079; *Ruzicka* and *Bosch*, Helv. **14**, 1336), can be cyclised to **bicyclo-isoprene-myrcene**, which, like cyclo-isoprene-myrcene, gives eudalene (p. 328) on dehydrogenation. These hydrocarbons, therefore, contain the following carbon skeletons:

Cyclo-isoprene-myrcene





Bicyclo-isoprene-myrcene

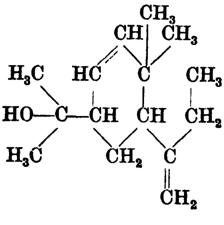
in which the positions of the double bonds are not yet certain. For the natural occurrence of cyclo-isoprene-myrcene in curcuma oil, see *Dieterle* and *Kaiser*, C. 1932 II 3739. An **isoamyl-α-dehydrophellandrene** has been synthesised from carvone and isoamyl Mg iodide (*Semmler*, *Jonas* and *Roenisch*, Ber. **50**, 430).

(b) **Alcohols.** — **Zingiberol**, $C_{15}H_{26}O$, b.p. 154–157°/14·5 mm., is contained with zingiberene in oil of ginger. With HCl and HBr it gives isozingiberene dihydrochloride and dihydrobromide respectively (*Brooks*, Am. **38**, 430).

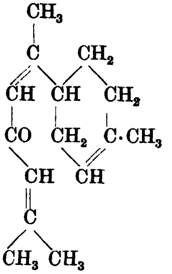
Elemol, $C_{15}H_{26}O$ (I, p. 326), m.p. 51–52°, b.p. 144–145°/15 mm., *phenylurethane* m.p. 112–113°, occurs in oil of Manila elemi, and contains a tertiary hydroxyl group. With Pt black it takes up 4 atoms of H, and hence contains two double bonds; one of these is present in a methylene group, which is split off by oxidation; the product is a ketonic alcohol, $C_{14}H_{24}O_2$, which contains one double bond. The dehydration of elemol gives **elemene**, $C_{15}H_{24}$, b.p. 115–117°/10 mm., which is a mixture; dehydrogenation of this or of elemol with S gives a thionaphthene derivative, $C_{14}H_{18}S$, and eudalene, whilst Se yields eudalene and an azulene (p. 330). This eudalene and the S-containing substance are formed as a result of ring-closure during dehydrogenation, since the further degradation of elemol has shown that it is a derivative of cyclohexene (*Ruzicka* and *van Veen,* Ann. **476,** 70).

Fokienol, $C_{15}H_{26}O$, b.p. 125–126°/2 mm., obtained from the wood oil of *Fokiena Hodginsii,* is a tertiary monocyclic sesquiterpene alcohol like elemol, but it gives cadalene on dehydrogenation (*Glichitch,* C. 1930 II 2070).

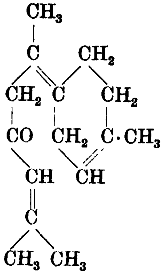
(c) **Ketones. — Atlantone,** $C_{15}H_{22}O$, from Atlas cedar oil, occurs in two forms, α- and γ-, the degradation products of which show that they correspond to α- and γ-bisabolene. If the CO group of atlantone is reduced by treating its semicarbazone with KOH, the resulting hydrocarbon gives bisabolene trihydrochloride on addition of HCl. When atlantone is boiled with alkali, acetone is lost (cf. the formation of acetone from pulegone, p. 235), and the following important degradation products are formed: **acetyl-dipentene** (IV), $C_{12}H_{18}O$, b.p. 125·5–126°/10 mm., *semicarbazone* m.p. 152·5–153° (or, from the γ-form, **acetyl-terpinolene,** *semicarbazone* m.p. 195–195·5°), and 1-methyl-4-acetyl-Δ^1-cyclohexene, $C_9H_{14}O$ (V), b.p. 84°/10 mm. The 4-methylcyclohexanone formed by the oxidation of the partially hydrogenated (α + γ)-atlantone is derived from the γ-form (*Pfau* and *Plattner,* Helv. **17,** 129). The ketone **turmerone,** $C_{15}H_{22}O$, which also contains three double bonds, is the odoriferous constituent of curcuma oil; it is very unstable and has not yet been obtained pure. It is converted very easily into a ketone $C_{15}H_{20}O$, *ar*-**turmerone** (VI), b.p. 159–160°/10 mm., $[\alpha]_D^{20}$ + 82·21°, *semicarbazone* m.p. 108–109°, a bright-yellow oil with an odour of spice; the ozonisation of this ketone yields acetone and curcumic acid (β, p-tolyl-butryic acid), $CH_3 \cdot C_6H_4 \cdot CH(CH_3) \cdot CH_2 \cdot COOH$, m.p. 43° (*Rupe, Clar, Pfau* and *Plattner,* Helv. **17,** 372; *Rupe* and *Gassmann,* Helv. **19,** 569). Fission of *ar*-turmerone with KOH yields curcumone and acetone.



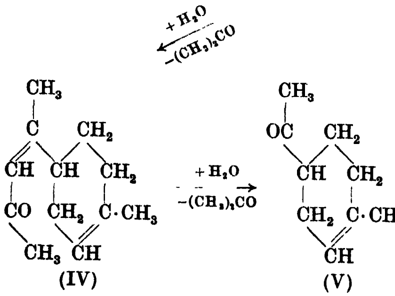
Elemol (I)



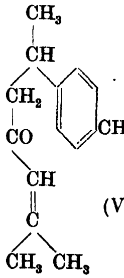
α-Atlantone (II)[1]



γ-Atlantone (III)[1]



(IV) (V)



(VI)

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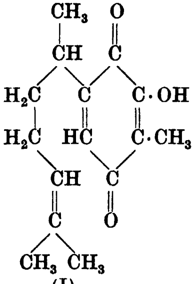
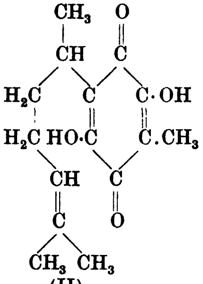
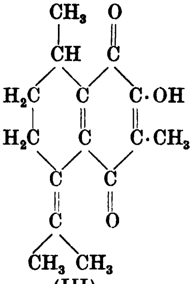
[1] Also contains some of the limonene form.

Perezone (I), $C_{15}H_{20}O_3$, m.p. 102–103°, $[\alpha^{20}_{D}]$ — 17·0° (in ether), is a bright yellow solid; it is obtained from the roots of the Mexican *Trixis Pipitzahuac* (*Compositae*), and is the first naturally occurring quinone of the sesquiterpene series to be isolated. With aniline it gives the deep violet *anilino-perezone*, $C_{21}H_{25}O_3N$, m.p. 135—136°, which is converted by acids into the red *hydroxyperezone* (II), $C_{15}H_{20}O_4$, m.p. 129°. With conc. sulphuric acid the latter is cyclised to the yellow cadalene derivative, **perezinone** (III), $C_{15}H_{18}O_3$, m.p. 143–145°. Perezone has been degraded via dihydro-perezone and hydroxy-dihydro-perezone to α,ε-dimethylheptoic acid, $(CH_3)_2{\cdot}CH{\cdot}(CH_2)_3{\cdot}CH(CH_3){\cdot}COOH$, while the ozonisation of hydroxy-perezone gives α,β-diketobutyric acid (*Kögl* and *de Boer*, Rec. **54**, 779; cf. also p. 422).


(I)


(II)


(III)

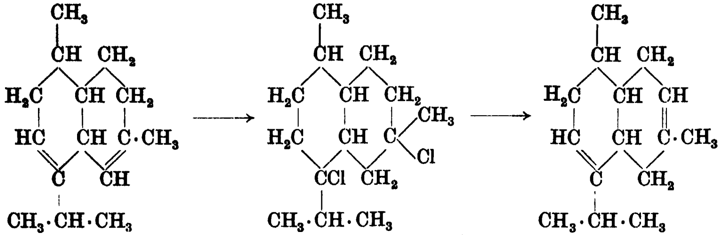
3. Bicyclic Sesquiterpenes.

— These can be placed in two groups, according to their behaviour when dehydrogenated.

1. Derivatives of hydrogenated naphthalenes; the hydrocarbon cadinene belongs to the cadalene type, while the eudalene type includes the hydrocarbon selinene, the alcohol eudesmol, the ketones eremophilone and α-cyperone, the lactones alanto- and isoalanto-lactone, and the ketonic lactones santonin and artemisin;
2. Derivatives of other ring-systems, such as caryophyllene.

(a) Hydrocarbons.

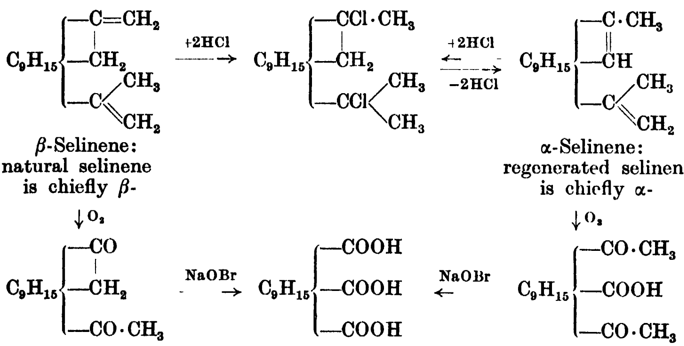
— **Cadinene,** b.p. 136°/11 mm.; d^{20}_4 0·9189; n^{20}_D 1·5079; $[\alpha]_{5461}$ — 125·2°, is found as both *d*- and *l*-forms in numerous essential oils, e.g. in *Oleum cadinum* (oil of cade), oil of cubebs, sandalwood oil, the oil of angostura bark, etc. With HCl it yields a *dihydrochloride*, m.p. 118°, which regenerates the hydrocarbon when warmed with aniline or sodium acetate. The *dihydrobromide* has m.p. 125°, and the *dihydriodide* m.p. 106°. Catalytic hydrogenation gives **tetrahydro-cadinene,** $C_{15}H_{28}$, b.p. 125–128°/10 mm. (*Semmler* and *Jonas*, Ber. **47**, 2068). Cadinene is formed by the dehydration of cadinol, a tertiary alcohol which occurs in galbanum oil (*Ruzicka* and *Stoll*, Helv. **7**, 94). The structure of cadinene is indicated by the fundamental observation that a naphthalene hydrocarbon, $C_{15}H_{18}$ is formed when it is dehydrogenated with Pt black in vacuo, or with sulphur or selenium (*Diels* and *Karstens*, Ber. **60**, 2323); this substituted naphthalene, **cadalene,** b.p. 158°/12 mm., d^{19}_4 0·9792, *picrate* m.p. 115°, *styphnate* m.p. 138°, has been shown to be *1:6-dimethyl-4-isopropylnaphthalene* by oxidative degradation and by synthesis (*Ruzicka, Meyer* and *Mingazzini*, Helv. **5**, 345; *Ruzicka* and *Seidel*, *ib.* 369). From these results and from the results of oxidation, the following two formulae must be allotted to cadinene; both give the same dihydro-halides. Both natural and regenerated cadinene are mixtures of α- and β-cadinene.



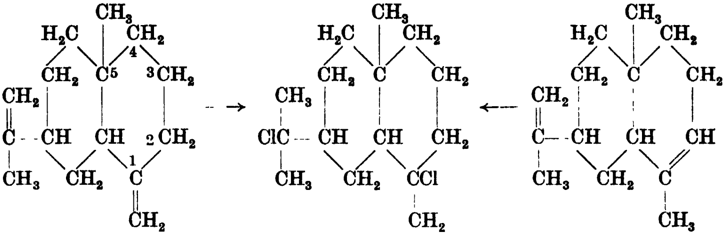
α-Cadinene Cadinene dihydrochloride β-Cadinene.

Kiganene, $C_{15}H_{24}$, b.p. 108–114°/4·5 mm., is a hydrocarbon very similar to cadinene; it is obtained from Japanese cedar oil. With HCl it gives cadinene dihydrochloride, and dehydrogenation yields cadalene. The occurrence of acetone amongst its products of ozonisation shows the presence of an isopropylidene group (*Kimura* and *Mizoshita,* Mem. Coll. Sci. Kyoto Imp. Univ. A, **14,** 273). See also isozingiberene, p. 325, and bicyclo-isoprene-myrcene, p. 325.

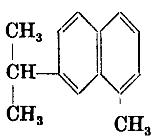
Selinene, b.p. 122°/6 mm., d^{18} 0·9170, is obtained from celery oil. Pt and H_2 give tetrahydroselinene, and HCl gives selinene *dihydrochloride,* $C_{15}H_{26}Cl_2$, m.p. 72–74°. The hydrocarbon regenerated from this dihydrochloride agrees well in its physical constants (with the exception of the rotation) with natural selinene, and can be reconverted into the dihydrochloride; it behaves differently, however, when degraded with ozone or treated with bromine and alkali (*Semmler* and *Risse,* Ber. **46,** 599), since one double bond occupies a different position in the regenerated substance. Natural selinene is degraded to a diketone, $C_{13}H_{20}O_2$, and then to a tricarboxylic acid, $C_9H_{15}(COOH)_3$; the same acid is obtained from regenerated selinene, but via a diketo-carboxylic acid, $C_{14}H_{22}O_4$:



The carbon skeleton is established by the conversion of both forms of selinene into eudalene by dehydrogenation with sulphur. **Eudalene,** $C_{14}H_{16}$, b.p. 143°/12 mm., d_4^{17} 0·9734, *picrate* m.p. 91°, *styphnate* m.p. 120° (*Ruzicka* and *Seidel,* Helv. **5,** 369), is *1-methyl-7-isopropylnaphthalene,* as shown by its synthesis from cuminaldehyde (*Ruzicka* and *Stoll,* Helv. **5,** 923; *Darzens* and *Lévy,* C. r. **194,** 2056). Only 14 of the 15 C-atoms of selinene are fixed by the formation of eudalene; the methyl group split out as CH_3SH in the sulphur dehydrogenation must be tertiary, and in order that the selinene molecule may be derived from three isoprene units this methyl group must be placed on C_5:

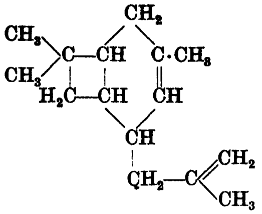


β-Selinene Selinene dihydrochloride α-Selinene

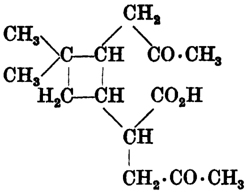


Eudalene

Caryophyllene, b.p. 128–134°/16 mm., d^{20} c. 0·9035, is the most widely distributed sesquiterpene in nature, with the exception of cadinene; its chief sources are oil of cloves, oil of the buds of clove blossoms, copaiba oil and hop oil (humulene is α-caryophyllene) (*Deussen*, J. pr. **120**, 133). It is a mixture of two isomeric hydrocarbons, which have not yet been obtained pure, but have been obtained in the form of derivatives. The optically inactive α-caryophyllene can be separated as *nitrosate*, m.p. 162°, *nitrosochloride*, m.p. 177°, or *nitrol-benzylamine*, m.p. 128°; the optically active β-caryophyllene is known as its *nitrosochloride*, m.p. 159°, *nitrol-benzylamine*, m.p. 173°, *nitrosite* (blue needles), m.p. 115°, and *dihydrochloride*, m.p. 70° (*Semmler* and *Mayer*, Ber. **43**, 3453). Both caryophyllenes have the same carbon skeleton, since they yield the same tetrahydro-derivative when reduced with H_2 and Pt (*Semmler* and *Mayer*, Ber. **45**, 1393). Caryophyllene gives no naphthalene derivative when dehydrogenated with S, and hence is not a hydrogenated naphthalene derivative (*Ruzicka, Stoll, Liebl* and *Pontalti*, Helv. **6**, 853). Degradation with ozone shows that the main constituent of caryophyllene most probably has the constitution (I) (*Ramage* and *Simonsen*, J. **1935**, 532). A *ketonic acid*, $C_{11}H_{18}O_3$ (*semicarbazone* m.p. 186–187°) is formed, together with a *diketonic acid*, $C_{14}H_{22}O_4$ (II), which is converted by bromine and alkali into the ketonic acid, $C_{14}H_{20}O_3$. Further degradation products are the *dicarboxylic acid*, $C_{13}H_{18}O_4$, m.p. 148–149°, the *ketonic dicarboxylic acid*, $C_{12}H_{18}O_5$, and *caryophyllenic acid* (IIIa or IIIb), $C_9H_{14}O_4$, m.p. (trans,*d*-form) 80–81°. From the latter the corresponding cis-acid, m.p. 78°, can be prepared; it has a small laevorotation (*Ramage* and *Simonsen*, J. **1936**, 741); the trans-acid was first obtained by oxidising the acid products of ozonolysis with HNO_3. Caryophyllenic acid was degraded via the α-bromo- and α-hydroxy-acids to *norcaryophyllenic acid* (IV, 3:3-dimethylcyclobutane-1:2-dicarboxylic acid), $C_8H_{12}O_4$ (trans-form m.p. 126°, cis-form m.p. 149–150°); this was converted to *dehydro-norcaryophyllenic acid* (3:3-dimethyl-Δ^1-cyclobutene-1:2-dicarboxylic acid) (V), $C_8H_{10}O_4$, m.p. 193°, which was oxidised to asymmetrical *dimethylsuccinic acid* (VI), $C_6H_{10}O_4$, m.p. 139–140°. Norcaryophyllenic acid has been synthesised from αα′-dibrom-ββ-dimethyladipic ester by ring closure with NaCN, hydrolysis and decarboxylation of the product, and converted into the dehydro-acid (V) (*Rydon*, J. **1936** 593).



(I)



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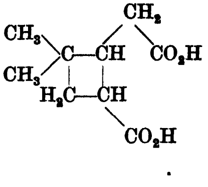
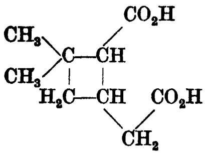
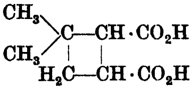


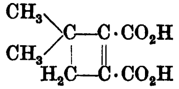
(IIIa)



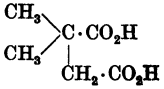
(IIIb)



(IV)



(V)



(VI)

Other caryophyllenes can be prepared by isomeric change from the natural hydrocarbon; an alcoholic solution of β-caryophyllene nitrosite gives on heating a hydrocarbon known as **γ-caryophyllene,** which is converted by HCl into the dihydrochloride of β-caryophyllene (*Deussen,* J. pr. **117,** 273). Treatment of a mixture of α- and β-caryophyllenes with acetic and sulphuric acids leads to hydration and cyclisation, with the formation of optically active *β-isocaryophyllene alcohol,* m.p. 95°, which contains a tertiary OH group; dehydration of this gives clovene (p. 335), a tricyclic hydrocarbon isomeric with caryophyllene.

β-Santalene occurs in the first runnings of East Indian sandalwood oil; see p. 333.

A series of hydrocarbons of the formula $C_{15}H_{18}$, deep-blue or violet in colour and known as the **azulenes,** appear to be closely related to the sesquiterpenes; their constitution is not yet fully explained. They are probably derivatives of bicyclo-[0:3:5]-decane, and contain 5 conjugated double bonds (*Pfau* and *Plattner,* Helv. **19,** 858). They are present in essential oils (in yarrow and camomile oils) and in lignite tar, and can be obtained by the dehydrogenation of guaiol or elemol with S or Se, and of kessyl alcohol with palladised charcoal (*Ruzicka* and *Haagen-Smit,* Helv. **14,** 1104; see also *Melville,* Am. **55,** 3288).

A large number of azulenes have been reported, but it appears that there are only four or five isomeric and distinct compounds. The separation is best carried out by fractional crystallisation of the picrates, or better, the more stable complexes with trinitrobenzene or trinitrotoluene. The following appear to be the chief compounds;

S-Guaiacazulene, m.p. 31·5 (*Birrell,* Am. **56,** 1248), *picrate* m.p. 122·5 , which occurs in geranium oil and can be obtained by S-dehydrogenation of the oils from guaiacum wood, etc.

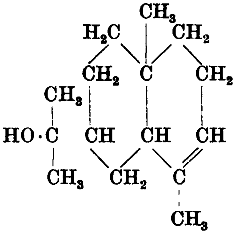
Camazulene, m.p. 132° (*Willstädt,* Ber. **69,** 999), from camomile oil, **lactarazulene,** a violet liquid isolated from the fungus *Lactarius deliciosus,* and **vetivazulene,** by the action of S on vetiver oil, resemble S-guaiacazulene in properties.

Elemazulene, a violet oil, *picrate* m.p. 110°, is obtained from elemol, a crystalline sesquiterpene alcohol mentioned above (p. 325), and from elemene with Se.

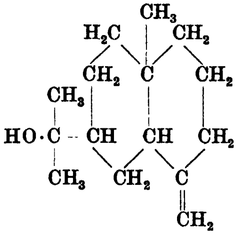
Se-Guaiacazulene, from the action of Se on guaiacum wood oil, has been shown to be a mixture from which S-guaiacazulene can be isolated.

For a review of the position of the azulene problem and for references, see *R. D. Haworth*, Ann. Rep. Chem. Soc. **84** (1937), 393.

(b) **Alcohols.** — **Eudesmol,** $C_{15}H_{26}O$, m.p. 84°, b.p. 156°/10 mm., is found in various eucalyptus oils, in the oil of a New Caledonian species of *Araucaria*, in Japanese machilus oil, in Japanese cedar root oil, etc. Eudesmol is a mixture of α- and β-compounds, the proportions of which vary according to the source; these correspond to α- and β-selinene; the m.p. and rotation are not much influenced by the relative quantities of α- and β-forms present.



α-Eudesmol ("*Selinenol*")



β-Eudesmol ("*Machilol*")

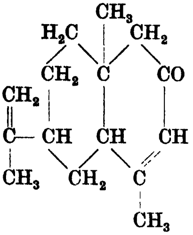
Dehydration gives selinene (*Ruzicka*, *Koolhaas* and *Wind*, Helv. **14**, 1178), and dehydrogenation with sulphur yields eudalene (p. 328).

Guaiol, $C_{15}H_{26}O$, m.p. 91°, b.p. 288°, is present in guaiacum wood oil (*Ruzicka*, *Pontalti* and *Balas*, Helv. **6**, 855; *Ruzicka* and *Haagen-Smit*, Helv. **14**, 1122). It can be reduced to *dihydroguaiol*, $C_{15}H_{28}O$, m.p. 79–80°. Formic acid yields *guaiene* $C_{15}H_{24}$, which has two reducible double bonds. Dehydrogenation of guaiol with S and with Se gives azulenes (see above). It is oxidised by $KMnO_4$ to a *dihydroxy-oxide*, $C_{15}H_{26}O_3$, m.p. 218°, which is converted by loss of $2H_2O$ into an *oxide*, $C_{15}H_{22}O$, b.p. 140–141°/15 mm.

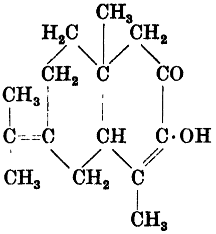
Kessyl alcohol, $C_{15}H_{26}O_2$, m.p. 85°; its *acetate*, m.p. 61°, is the characteristic constituent of Japanese valerian or kesso root oil. It is a bicyclic, saturated secondary alcohol containing an oxide ring. Dehydrogenation leads to a deep-blue azulene (*kessazulene*) and to *desoxykessylene* $C_{15}H_{22}$ (*Asahina* and *Nakanishi*, J. Pharm. Soc. Japan **52** (1932), 1). Oxidation of kessyl alcohol gives **kessyl ketone,** $C_{15}H_{24}O_2$, m.p. 105°, which is reduced by sodium and alcohol to **isokessyl alcohol,** $C_{15}H_{26}O_2$, m.p. 118–119°. Several isomeric kessyl alcohols have been prepared, either by direct rearrangement of kessyl alcohol, or from isomeric kessyl ketones; they owe their formation to the ease of rearrangement of the following grouping:

$$—CH_2·\overset{*}{C}H(OH)·\overset{*}{C}H< \quad (^{*}\text{centre of asymmetry})$$

(c) **Ketones.** — **Eremophilone,** $C_{15}H_{22}O$ (I), m.p. 42–43°, b.p. 171°/15 mm., d^{25}_{25} 0·9994, $[\alpha]_D$ — 171·6°, *semicarbazone* m.p. 202–203°, is obtained from the wood oil of *Eremophila Mitchellii*. It contains two double bonds and also the group $—CO·CH_2—$, since it gives a hydroxymethylene compound. Na and alcohol reduce it to *dihydroeremophilol*, $C_{15}H_{26}O$, b.p. 168–170°/14 mm., which gives eudalene when dehydrogenated with Se; this shows that eremophilone belongs to the eudalene type. Cautious oxidation of eremophilone with alkaline H_2O_2 gives *eremophilone oxide*, from which **hydroxy-eremophilone,** $C_{15}H_{22}O_2$ (II), m.p. 66–67° (*benzoate* m.p. 119–120°) is obtained; the latter accompanies eremophilone in the wood oil. Another compound also present is the hydroxy-ketone, **hydroxy-dihydro-eremophilone** (III), $C_{15}H_{24}O_2$, m.p. 102–103°, *2:4-dinitrophenylhydrazone* m.p. 239–241°, *diacetate* of the enol-form m.p. 69–70°; this can be reduced to tetrahydro-eremophilone, and dehydrogenated to eudalene. The structures of these compounds are not known with certainly.



(I)



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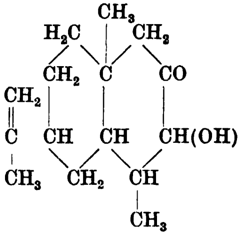
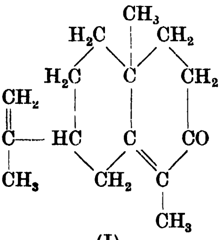


(III)

The constitution of the side-chain has been deduced from the presence of HCHO or $(CH_3)_2CO$ in the ozonolysis products (*Bradfield, Penfold* and *Simonsen,* J. **1932,** 2744; *idem,* Proc. Roy. Soc. New South Wales **66,** 420). The ketone **zierone,** $C_{15}H_{22}O$, b.p. 147–149°/18 mm., *semicarbazone* m.p. 182°, obtained from the oil of *Zieria macrophylla,* is isomeric with eremophilone, but is tricyclic and hence contains only one double bond (*Bradfield, Penfold* and *Simonsen,* Proc. Royal Soc. N. S. W. **67,** 200).

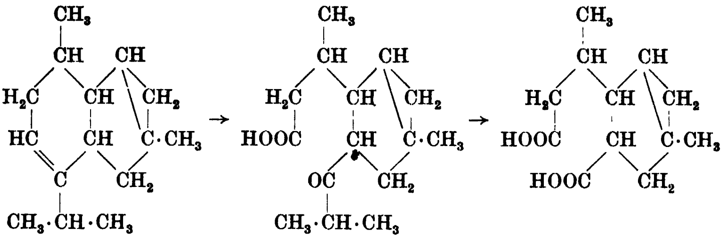
α-Cyperone, $C_{15}H_{22}O$, b.p. 177°/20 mm., *semicarbazone* m.p. 216°, *oxime* m.p. 150·5°, is contained in the oil from *Cyperus rotundus*; hydrogenation yields *dihydro-α-cyperol,* which is dehydrogenated by Se to eudalene (*Bradfield, Hedge, Rao* and *Simonsen,* J. **1936,** 667). This ketone probably has the structure (I) (*Bradfield, Pritchard* and *Simonsen,* J. **1937,** 760). It is converted into *β*-cyperone (probably a stereoisomer) by long treatment with oxalic or phthalic acid.



(I)

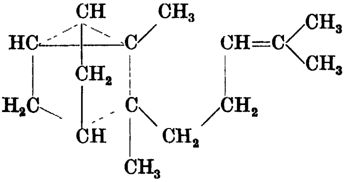
(d) **Lactones.** — **Alantolactone,** $C_{15}H_{20}O_2$, m.p. 71°, and **isoalantolactone,** m.p. 116°, **dihydro-isoalantolactone,** $C_{15}H_{22}O_2$, m.p. 168°, and the ketonic lactone **santonin,** $C_{15}H_{18}O_3$, m.p. 170°, have the carbon skeleton of the eudesmol group of sesquiterpenes. They are dealt with under natural products, p. 486.

4. Tricyclic Sesquiterpenes. — (a) **Hydrocarbons. Copaene,** $C_{15}H_{24}$ (I), b.p. 120°/10 mm., d^{15} 0·9077, n_D 1·4894, $[\alpha]_D$ — 13·21°, is found in African oil of copaiba (*Semmler* and *Stenzel,* Ber. **47,** 2555) and in oil of supa (*Henderson, M'Nab* and *Robertson,* J. **1926,** 3077). It has the carbon skeleton of cadinene, but differs from it in that the ring with only one side-chain is bridged to form a three-membered ring instead of containing a double bond. HCl gives cadinene dihydrochloride, and dehydrogenation with S yields cadalene. Oxidation with $KMnO_4$ or with O_3 gives **ketocopaenic acid,** $C_{15}H_{24}O_3$ (II) (*semicarbazone* m.p. 221°), which is degraded by hypobromite to **copaene-dicarboxylic acid,** $C_{12}H_{18}O_4$ (III) (*dimethyl ester* b.p. 178–182°/17 mm.):

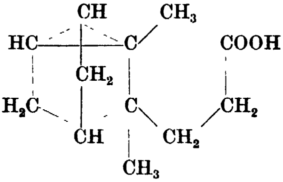


(I) (II) (III)

α-Santalene, $C_{15}H_{24}$, b.p. 118–120°/9 mm., d^{20} 0·8984, n_D 1·491, and **β-santalene,** $C_{15}H_{24}$, b.p. 125–127°/9 mm., d^{20} 0·892, n_D 1·4932, are contained in the first runnings of sandalwood oil; the former is a tricyclic sesquiterpene, and the latter bicyclic. α-Santalene (I) (*nitrosochloride* m.p. 122°) gives on ozonolysis the aldehyde **tricyclo-eksantalal,** $C_{12}H_{18}O$, b.p. 110°/9 mm., which can be oxidised to **tricyclo-eksantalic acid,** $C_{12}H_{18}O_2$ (II), m.p. 69°; further degradation gives the tricyclic **nor-eksantalic acid** (III), $C_{11}H_{16}O_2$, m.p. 93°, and then **teresantalic acid** (IV) (see p. 275) (*Semmler* Ber. **43**, 1893; *Ruzicka* and *Liebl*, Helv. **9**, 140). β-Santalene forms two *nitrosochlorides*, m.ps. 152° and 106°; it has a double bond in place of the three-membered ring, and is perhaps related to α-santalene as camphene is to tricyclene (*Ruzicka* and *Thomann*, Helv. **18**, 355).



(I)



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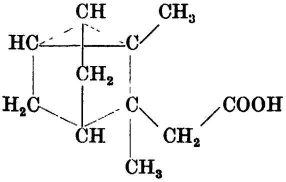

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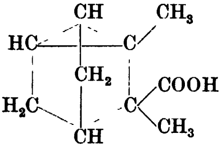
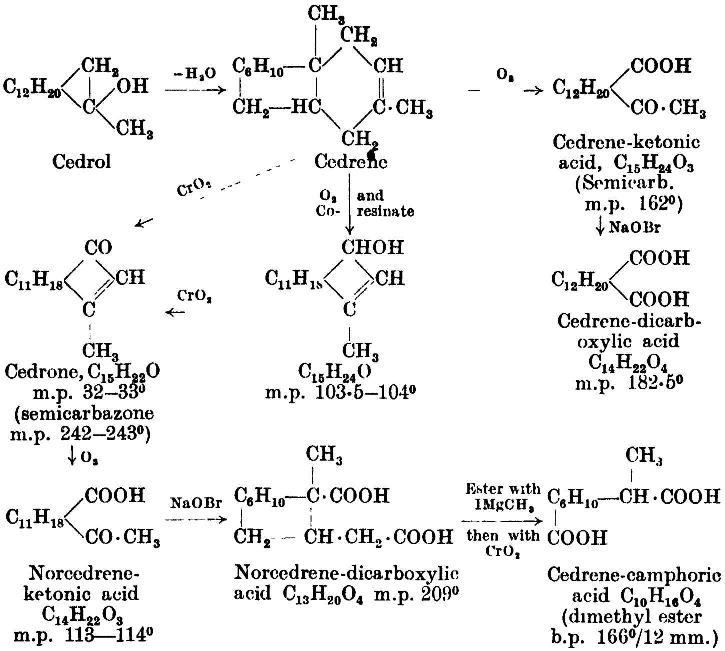
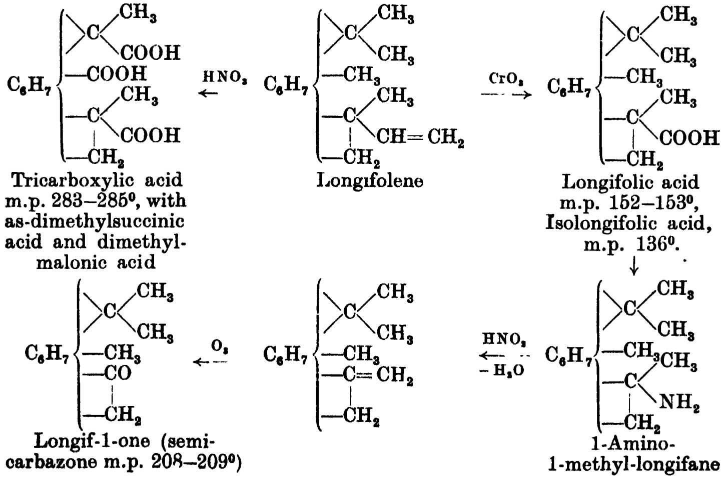


(IV)

Cedrene, $C_{15}H_{24}$, b.p. 124°/12 mm., occurs in the cedar wood oil of *Juniperus virginiana* and in the oil from *Dacrydium elatum*; **cedrol,** $C_{15}H_{26}O$, is also present and can be dehydrated to cedrene (*Rabak*, C. 1929 I 2710). Cedrene gives a very characteristic *glycol*, $C_{15}H_{28}O_2$, m.p. 168°, with $KMnO_4$, and this serves for its identification. Cedrene adds two atoms of Br, but does not give a naphthalene derivative when dehydrogenated with S (*Deussen*, J. pr. **117**, 290; *Ruzicka* and *van Melsen*, Ann. **471**, 40; *Blumann* and *Schulz*. Ber. **64**, 1540). The following formulae show the more important degradations of cedrene (*Ruzicka* and *Jutassy*, Helv. **19**, 322).


Cedrol
-H₂O
Cedrene
O₂
Cedrene-ketonic acid, C₁₅H₂₄O₃ (Semicarb. m.p. 162°)
CrO₃
O₂ Co-resinate and
NaOBr
Cedrene-dicarboxylic acid C₁₄H₂₂O₄ m.p. 182·5°
Cedrone, C₁₅H₂₂O m.p. 32–33° (semicarbazone m.p. 242–243°)
CrO₃
C₁₅H₂₄O m.p. 103·5–104°
O₃
NaOBr
Ester with 1MgCH₃ then with CrO₃
Norcedrene-ketonic acid C₁₄H₂₂O₃ m.p. 113—114°
Norcedrene-dicarboxylic acid C₁₃H₂₀O₄ m.p. 209°
Cedrene-camphoric acid C₁₀H₁₆O₄ (dimethyl ester b.p. 166°/12 mm.)

Longifolene, $C_{15}H_{24}$, b.p. 266°/706 mm., d_{30}^{30} 0·9284, n_D^{30} 1·495, $[\alpha]_D$ + 42·73°, is found in the turpentine oil from *Pinus longifolia*: *hydrochloride* m.p. 60° (*Simonsen,* J. **123**, 2642), *hydrobromide* m.p. 69–70°, *hydriodide* m.p. 71°. It is tricyclic and contains one double bond. The various degradations carried out upon it can be shown as follows (*Bradfield, Francis* and *Simonsen,* J. **1934**, 188):

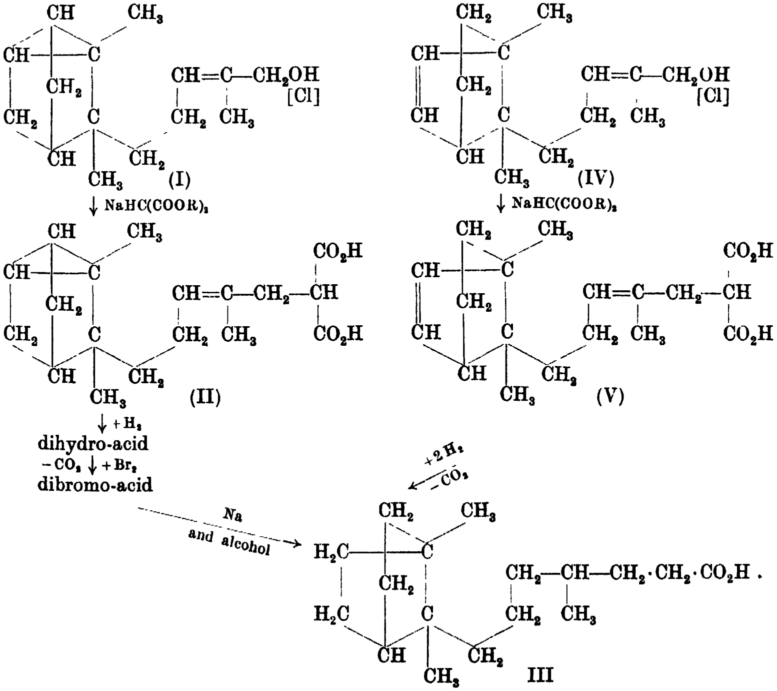

Tricarboxylic acid m.p. 283–285°, with as-dimethylsuccinic acid and dimethylmalonic acid
HNO₃
Longifolene
CrO₃
Longifolic acid m.p. 152–153°, Isolongifolic acid, m.p. 136°.
Longif-1-one (semicarbazone m.p. 208–209°)
O₃
HNO₂ -H₂O
1-Amino-1-methyl-longifane

The vinyl side-chain is an interesting feature (cf. sclareol and pimaric acid).

Clovene is obtained by the action of acids upon caryophyllene; it is oxidised by CrO_3 to **clovenic acid,** $C_{15}H_{24}O_4$, m.p. 182°, *anhydride* m.p. 50–51° (*Haarmann,* Ber. **42**, 1062; *Bell* and *Henderson,* J. **1930**, 1971; *Ruzicka* and *Gibson,* Helv. **14**, 570).

Gurjunene is obtained from gurjun balsam (*Semmler* and *Jakubowitz,* Ber. **47**, 2252; *Treibs,* Ber. **68**, 1751; *Ruzicka, Pontalti* and *Balas,* Helv. **6**, 855). For **vetivene,** see *Ruzicka, Capato* and *Huyser,* Rec. **47**, 370.

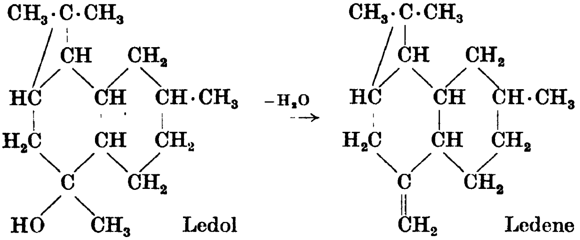
(b) **Alcohols.** — **Santalol,** $C_{15}H_{24}O$, is the main constituent of East Indian sandalwood oil (from *Santalum album*) and of Australian sandalwood oil (from *Santalum spicatum*) (*Swallow,* J. Amer. Pharm. Assoc. **18**, 683). It is a mixture of two unsaturated primary alcohols, the tricyclic α-**santalol** (I), b.p. 166–167°/14 mm., d_{25}^{25} 0·9770, n_D^{25} 1·5017, *allophanate* m.p. 162–163° (*Bradfield, Penfold* and *Simonsen,* J. **1935**, 309), and the bicyclic β-**santalol** (IV), b.p. 177–178°/17 mm., d_{25}^{25} 0·9717, n_D^{25} 1·5100, *allophanate* m.p. 159–160°. Oxidation of α-santalol yields the same degradation products as those obtained from α-santalene. Acids convert α-santalol and its derivatives into bicyclic compounds (*Semmler,* Ber. **43**, 1893). α- and β-Santalol can be converted into the same *tetrahydro-santalylacetic acid* (III) (*p-bromphenacyl ester,* m.p. 52–53°) in the following way. α-Santalol is converted into its chloride and condensed with sodio-malonic ester to yield the acid (II), which is hydrogenated and decarboxylated; addition of bromine opens the three-membered ring to give a dibromo-acid, which is reduced with Na and alcohol to (III). β-Santalol is converted into its chloride and condensed with sodio-malonic ester to give the acid (V), which is hydrogenated and decarboxylated to yield the acid (III). These reactions show clearly the relationship between α- and β-santalol (*Bradfield, Penfold* and *Simonsen,* l. c.):



Santalol is used therapeutically in the treatment of gonorrhoea: "*gonorol*" is a trade name for santalol, and many of its esters and ethers are likewise used, e.g. "*santyl*", the salicylic ester, "*blenal*", the carbonate, "*camphoral*", the camphoric ester, "*camphosan*", the camphoric methyl ester, "*stearosan*", the stearic ester, "*allosan*", the allophanate, "*thyresol*", the methyl ether, "*gonosan*", 80% santalol and 20% Kawa resin (cf. p. 434), etc.

Cedrol, $C_{15}H_{26}O$, m.p. 86°, *phenylurethane* m.p. 107°, is found in cedar-wood oil (see p. 333), in cypress oil from *Cupressus sempervirens* L., and in several other oils; it is dehydrated to cedrene (*Semmler* and *Spornitz*, Ber. **45**, 1553). **Cedrenol,** $C_{15}H_{24}O$, b.p. 166–169°/9·5 mm., obtained from cedar-wood oil, is a primary alcohol which can converted via its chloride into cedrene; it is related to cedrene as myrtenol is to α-pinene (*Semmler* and *Mayer*, Ber. **45**, 786).

Ledol, *Ledum camphor*, $C_{15}H_{26}O$, m.p. 105°, is a tertiary alcohol, which appears to be a carane compound of the sesquiterpene series (*Komppa*, C. 1953 II 3121). It can be dehydrated to ledene $C_{15}H_{24}$, which gives cadalene and an azulene when dehydrogenated with Se.



Ledol Ledene

Patchouli alcohol, $C_{15}H_{26}O$, m.p. 56°, is a tricyclic tertiary alcohol, which separates in crystals from patchouli oil (*Wallach*, Ann. **279**, 394; *Gadamer* and *Amenomiya*, Arch. Pharm. **241** (1903), 39; *Wienhaus*, Ber. **47**, 330).

Sesquicamphenol, $C_{15}H_{26}O$, b.p. 159–162°/7 mm., from oil of camphor, is a mixture of primary, secondary and tertiary alcohols with different carbon skeletons (*Ruzicka* and *Stoll*, Helv. **7**, 260).

Bulnesol, $C_{15}H_{26}O$, m.p. 69–70°, is a constituent of guaiacum wood oil (*Wienhaus* and *Scholz*, Sch. & Co. Bericht (Jubil.-Ausg.) **1929**, 267).

Betulol, $C_{15}H_{24}O$, is a constituent of the oil from the leaf buds of *Betula alba* L. (*v. Soden* and *Elze*, Ber. **38**, 1636); it is also present in the oil from birch buds (*Treibs*, Ber. **69**, 41).

The **diterpenes,** $C_{20}H_{32}$, and the **polyterpenes,** $(C_5H_8)_x$, are yellow viscous oils boiling above 300°; they are scarcely volatile with steam and hence are seldom met with in essential oils. They are present in many balsams and resins. Their characterisation is made difficult by the fact that they do not readily form crystalline addition products. While the sesquiterpenes appear to be built up from a regular arrangement of isoprene units, an irregular arrangement seems to be more general in the diterpenes (*Ruzicka, Goldberg, Huyser* and *Seidel*, Helv. **14**, 545). Some of these higher terpenes have been dehydrogenated to aromatic substances, e.g. to retene and pimanthrene; from some pentacyclic triterpenes 1:8-dimethyl-picene has been obtained and also various substituted naphthalenes and 1:2:3:4-tetramethylbenzene (*Ruzicka, Hoffmann* and *Schellenberg*, Helv. **19**, 1391).

For a review of work in the triterpene group, see *R. D. Haworth*, Ann. Rep. Chem. Soc. **34** (1937), 327.

α-Camphorene, $C_{20}H_{32}$, b.p. 178°/6 mm., d^{20} 0·8870, n_D 1·50339, has been isolated from oil of camphor. It is monocyclic and contains 4 double bonds; its *tetra-hydrochloride*, $C_{20}H_{36}Cl_4$, has m.p. 129–131°, and the original hydrocarbon can be regenerated from it. Catalytic hydrogenation gives an octahydride, $C_{20}H_{40}$. α-Camphorene, accompanied by **γ-camphorene** (*tetra-hydrochloride* m.p. 96–98°), can be synthesised from myrcene and linalool (*Semmler* and *Jonas*, Ber. **47**, 2077; *Kafaku, Oyamada* and *Nishi*, Bull. Chem. Soc. Japan **8** (1934), 144). For its constitution see *Ruzicka* and *Stoll*, Helv. **7**, 271; *Ruzicka* and *Bosch*, Helv. **14**, 1336.

The following are well characterised, but their constitution is not yet known: **α-cryptomerene,** $C_{20}H_{32}$, m.p. 61°, b.p. 345°, from the oil from the leaves of *Cryptomeria japonica* (*Uchida*, Am. **38**, 687), and **dacrene,** $C_{20}H_{32}$, m.p. 91°, from the oil of the leaves of *Dacrydium biforme* (*Goudie*, Chem. and Ind. **42**, 357 T). Boiling with formic acid converts dacrene into **isodacrene,** m.p. 107° (*Blackie*, Chem. and Ind. **49**, 26 T). Isodacrene is obtained in a similar way from **rimuene,** $C_{20}H_{32}$, m.p. 55°, the diterpene from *Dacrydium cupressinum*; *hydrochloride*, $C_{20}H_{33}Cl$, m.p. 63°. Dehydrogenation yields *isoretene* $C_{18}H_{18}$, m.p. 86–87° (*picrate* m.p. 127°), a phenanthrene derivative in which the position of the side-chains is unknown (*Beath*, Chem. and Ind. **53**, 338 T). **Kaurene** and **mirene,** both $C_{20}H_{32}$, are tetracyclic and contain one double bond; dehydrogenation with S gives pimanthrene (p. 348) (*Hosking*, Rec. **49**, 1036).

α- and **β-Podocarprene,** $C_{20}H_{32}$, have m.p. 50° and b.p. 188–190°/9 mm. respectively (*Nishida* and *Uota*, C. 1932 I 2028).

Josene, $C_{20}H_{34}$, m.p. 74°, which occurs in Austrian lignite as the organic mineral "*hartite*", is closely related to fichtelite and abietic acid, since dehydrogenation with Se gives retene (*Soltys*, Mo. **53/54**, 185).

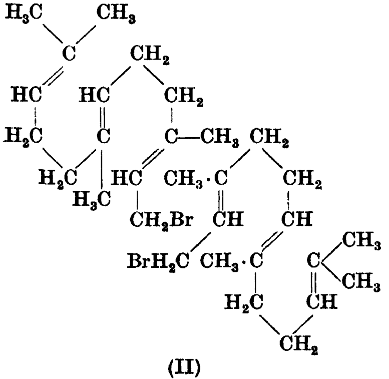
Phytol, $C_{20}H_{40}O$; see I 152.

1-(**β-Cyclogeranyl**)-**geraniol,** $C_{20}H_{34}O$, has been obtained synthetically (*Ruzicka* and *Fischer*, Helv. **17**, 633).

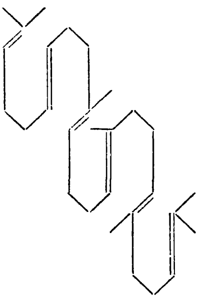
Sclareol, $C_{20}H_{36}O_2$, m.p. 106°, is a bicyclic dihydroxy derivative of a diterpene with a vinyl group, and contains only one double bond (*Ruzicka* and *Janot*, Helv. **14**, 645). Dehydrogenation with S gives, amongst other products, 1:2:5-trimethylnaphthalene, as in the case of tetracyclosqualene. Oxidation yields *sclareolic acid*, $C_{19}H_{24}O_4$, m.p. 153–155°.

Manool, $C_{20}H_{34}O$, m.p. 56°, gives with HCl the same *trihydrochloride*, $C_{20}H_{35}Cl_3$, m.p. 119°, as that obtained from sclareol (*Hosking*, Ber. **69**, 780); it is related to sclareol as α-terpineol is to terpin hydrate.

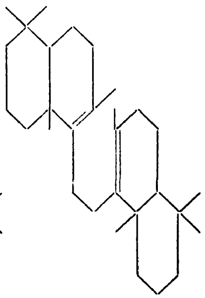
Squalene (I), $C_{30}H_{50}$, b.p. 254°/5 mm., d_4^{15} 0·8587, n_D^{20} 1·4965, occurs in the liver-oils of fishes (*Tsujimoto* and *Kimura*, J. Soc. Chem. Ind. Japan **30**, 341). Its structure is symmetrical, and is made up of an irregular arrangement of six isoprene residues, as is shown by its synthesis from two molecules of farnesyl bromide (II) and magnesium (*Karrer* and *Helfenstein*, Helv. **14**, 78):



(II)
2 Mol. Farnesyl bromide



(I)
Squalene



(III)
Tetracyclosqualene

It forms two distinct *hexahydrochlorides*: m.p. 145° (insoluble in acetone), and m.p. 110° (soluble in acetone) (*Heilbron* et al. J. **1926**, 1630). In presence of acids it undergoes isomeric change to **tetracyclosqualene** (III), the dehydrogenation of which yields 1:2:5-trimethylnaphthalene (*agathalene, Ruzicka* and *Ehmann*, Helv. **15**, 140).

α-Amyrin, m.p. 184°, and **β-amyrin,** m.p. 194°, are two triterpene alcohols, $C_{30}H_{50}O$, which are obtained together with elemol and elemolic acid from Manila elemi resin. *α-Amyrin benzoate* has m.p. 194–195°, *β-amyrin benzoate* m.p. 230–231°. Both amyrins can be oxidised with CrO_3 to ketones, $C_{30}H_{48}O$: **α-amyrone,** m.p. 125–126° (*semicarbazone* m.p. 205–206°), and **β-amyrone,** m.p. 177–178° (*semicarbazone* m.p. 244–245°). Both amyrins contain one double bond, which is not reactive in α-amyrin, but reactive in β-amyrin. The following substances have been isolated from the Se dehydrogenation: (a) 1:2:7-trimethylnaphthalene, *sapotalene*, $C_{13}H_{14}$, b.p. 143°/13 mm. (*picrate* m.p. 129°) (synthesis: *Ruzicka* and *Ehmann*, Helv. **15**, 140; *Späth* and *Hromatka*, Mo. **60**, 117); (b) 1:2:5:6-tetramethyl-naphthalene, m.p. 116° (*picrate* m.p. 156–157°); (c) 1:8-dimethyl-picene, m.p. 304–305°; (d) hydroxy-sapotalene $C_{13}H_{14}O$, m.p. 156–157° (*benzoate* m.p. 185°). Ozonolysis of α-amyrin gives the ketone **α-amyranone,** $C_{27}H_{42}O$, m.p. 94–96°, by loss of an isopropyl group (*Dieterle* and *Salomon*, C. 1933 I 3453). For hydrocarbons from the amyrins see *Winterstein* and *Stein*, Ann. **502**, 223. **Lupeol,** $C_{30}H_{50}O$, m.p. 212–213°, isolated from lupin seeds, is an unsaturated alcohol with one double bond. CrO_3 gives a ketone **lupone,** $C_{27}H_{42}O$, m.p. 170° (cf. the formation of amyranone from amyrin) (*Dieterle* and *Salomon*, C. 1933 I 1297). **Betulin,** $C_{30}H_{50}O_2$, m.p. 251°, occurs in the bark of the birch; on dehydrogenation it gives several products which include 1:2:3:4-tetramethylbenzene, sapotalene (see above), 1:2:5:6-tetramethylnaphthalene, 1:8-dimethyl-picene, and a picene $C_{25}H_{20}$, m.p. 324° (*Ruzicka, Brungger, Egli, Ehmann* and *Goldberg*, Helv. **15**, 1496; *Ruzicka, Frame, Leicester, Liguori* and *Brüngger*, Helv. **17**, 426; *Ruzicka* and *Isler*, Helv. **19**, 506).

Rubber[1], $(C_5H_8)_x$, a very important raw material in many branches of industry, is found in the milky sap (*latex*) of numerous tropical plants.

The following yield rubber: *Euphorbiaceae* (*Hevea brasiliensis, Manihot Glaziovii*), *Apocynaceae, Moraceae* (*Castilloa elastica*) etc., and also various species of *Liana* (Africa) and of *Ficus* (*Ficus elastica*, India). The greater part of the rubber of commerce to-day is obtained from plantations, in particular from cultivated *Hevea brasiliensis*. It is the rubber from this plant that has been most investigated. For guaiula-rubber from the Composita *Parthenium argentatum*, see *Lloyd*, Plant Physiol. **7**, 131; U.S.A. Pat. 1,918,671 (1928).

The technical preparation of rubber. — The milky sap obtained from the plants by slitting the bark contains, besides suspended particles of rubber, a whole series of other substances such as sugars, proteins, resins and inorganic salts; these are partly in colloidal solution and can be completely separated from the rubber only with great difficulty. The rubber is separated from the sap by coagulation, either by subjecting it in thin layers on wood to the smoke of resinous plants (the Brazilian method), by drying thin layers of latex in the air, or by precipitation, e.g. with acids, such as formic or acetic acid (the method used in Asia). Latex itself is put on the market, either in its original form with the addition of a little ammonia, etc., to prevent coagulation, or reduced to the form of paste by a special process which involves the addition of a protective colloid; this paste can be converted by addition of water into a latex of any desired concentration, and is called "revertex", i.e. reversible latex (*Hauser*, Kautschuk **1927**, 17).

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[1] See, "The Chemistry and Technology of Rubber", ed. *C. C. Davis* and *J. T. Blake*, American Chem. Soc. Monographs. *H. Barron*, "Modern Rubber Chemistry", Hutchinson, London 1937.

The coagulated rubber is then macerated, and worked by rolling until it becomes plastic, and in this state it can be mixed with fillers (soot, etc.), pigments, sulphur, etc. During this process it loses some of its elasticity, but this is recovered during vulcanisation: the molecular size becomes smaller during the maceration, but is increased again by the vulcanisation. To give the rubber greater elasticity and tensile strength, and to make it more resistant to air and light, it is treated with sulphur, either in the cold by immersion in S_2Cl_2-solutions (cold vulcanisation) or at 110—145° with elementary sulphur (hot vulcanisation). The chemical effect of vulcanisation consists of an enlargement of the molecule, either by the linking together of two or more molecules of rubber by means of sulphur atoms (cf. the formation of $\beta\beta'$-dichloro-diethyl sulphide from ethylene and S_2Cl_2; see also *Meyer* and *Mark*, Ber. **61**, 1948), or by the condensation of two or more molecules of rubber as a result of activation of the double bonds. The latter type of enlargement of the molecule is also caused by the action of light, and can be accelerated by the use of catalysts (*Pummerer* and *Kehlen*, Ber. **66**, 1107; Brit. Pat. 389,637 (1932); U.S.A. Pat. 1,906,314 (1931)). In the same way the molecular enlargement in vulcanisation can be carried out more quickly and at a lower temperature in the presence of certain substances which are called accelerators; the chief substances used for this purpose are bases of different types, e.g. hexamine, (cf. *Oenslager*, Chem. and Ind. **52**, 91), guanidine derivatives (diphenyl-guanidine), and sulphur-containing compounds, e.g. 2-mercapto-benzthiazole, mercapto-benzthiazole-disulphide (*Seide* and *Petrov*, C. 1936 I 203). In the course of time rubber loses its elasticity ("perishes"); this is largely due to oxidation, and hence protective substances (anti-oxidants, cf. also *Bondy*, Ber. **66**, 1611; *Dufraisse* and *Drisch*, C. 1931 II 3278) are added, chiefly amino-compounds which have been found experimentally to fulfil this function. The soft rubber obtained by the addition of small quantities of sulphur has many uses for the preparation of tubing, tyres, sheet-rubber, waterproof-material, driving belts, flooring, etc.

"*Vultex*" (vulcanised latex) is a suspension of vulcanised rubber particles in unchanged serum (Brit. Pat. 266,418 [1925]; *Schidrowitz*, Kautschuk **1927**, 202). "*Revultex*" is the vulcanised product corresponding to revertex.

If the sulphur treatment of rubber is taken so far that approximately one atom of S is taken up by each C_5H_8-group, hard rubber is obtained, an insoluble, inelastic, very resistant mass, which has found many uses because of its insensitivity to acids and the ease of its preparation. In hard rubber there are probably three-dimensional macro-molecules formed by the condensation of rubber molecules in all three directions, with or without the aid of S-atoms (see, e.g., *Staudinger* and *Joseph*, Ber. **63**, 2890). The regeneration of old rubber is an important technical problem.

Rubber which is to be used for scientific investigation must be most carefully purified from the inorganic salts and nitrogenous substances which cling tenaciously to it, and must be protected from the action of air and light. By treatment with ether, rubber can be separated into an easily soluble part (sol-rubber) and an almost insoluble part (gel-rubber), which show no chemical differences (*Pummerer*, *Andriessen* and *Gündel*, Ber. **61**, 1583); their formation, however, shows that rubber is not a single chemical substance, but a mixture of hydrocarbons of high molecular weight, which differ from each other by multiples of C_5H_8, i.e. are *polymeric homologues.*

Rubber is amorphous, but gives an X-ray diagram when it is stretched; this vanishes again when the rubber contracts (*Katz*, Nature **13**, 710) (see also p. 343). The same X-ray diagram is also shown by rubber that has been "frozen" for a long time at a low temperature (*Katz*, Z. angew. Chem. **38**, 439). Both these results indicate that rubber can become crystalline (*van Rossem* and *Lotichius*, C. 1929 I 1517). The first isolation of crystals of rubber was achieved by cooling an ethereal solution of sol-rubber to — 60°: m.p. 9·5—11° (*Smith*, *Saylor* and *Wing*, Bureau Standards J. Res. **10**, 479).

The **distillation** of rubber at temperatures above 300° causes decomposition and numerous hydrocarbons are formed. In the low-boiling portion there are found isoprene (I, 116), in quantities up to 22·7% (*Bassett* and *Williams*, J. **1932**, 2324), and trimethylethylene (*Ipatiev* and *Wittorf*, J. pr. **55**, 2). Dipentene is found in the higher fractions (*Wallach*, Ann. **227**, 293), but it is not a primary decomposition product of rubber and is formed by the polymerisation of isoprene (see also p. 345); the same is true for the higher hydrocarbons $C_{15}H_{24}$, $C_{20}H_{32}$, and $C_{25}H_{40}$, all of which are cyclic (*Staudinger* and *Fritschi*, Helv. **5**, 785). The residue is a brittle resin, *cyclo-rubber*, a rearrangement product of rubber, which is also obtained without any low-boiling decomposition products by heating rubber to 250°; in this cyclo-rubber only one double bond can be found per five C_5H_8-groups, and hence four C_5H_8-groups have been cyclised (*Staudinger* and *Widmer*, Helv. **9**, 545) (see also cyclo-rubber from the hydrochloride). Cyclo-rubber decomposes only above 350°; cyclic compounds are formed, but no dipentene can be found among them.

In the presence of aluminium chloride the thermal decomposition of rubber takes place at a lower temperature; cyclic products are formed, but no isoprene (*Zelinsky* and *Koslov*, Ann. **497**, 160). The distillation of rubber at 700° gives also aromatic hydrocarbons (*Midgley jun.* and *Henne*, Am. **51**, 1215).

When rubber is treated with **ethylenic reagents,** one double bond can be detected for each C_5H_8-group; an example is iodine chloride, which can be used for the quantitative estimation of the double bonds (*Pummerer* and *Stark*, Ber. **67**, 292). With bromine, rubber forms a white insoluble substance, *rubber dibromide* $(C_5H_8Br_2)_x$, which loses HBr on heating (*Weber*, Ber. **33**, 786), and has been used for the synthesis of hydroxyphenyl-derivatives of rubber (*Geiger*, Helv. **10**, 530, 539). The corresponding dichloride is not obtained by the action of chlorine, since HCl is split off at once and substitution takes place. A derivative of rubber obtained by the energetic action of chlorine, perhaps containing some $(C_5H_6Cl_4)_x$, has technical uses ("*tornesite*", *Fol* and *Bijl*, Chem. Weekblad **29**, 162;

Rinse, ib. 521; *Rosendahl,* Ch. Ztg. **59**, 729; see also chlorinated rubber, *Kirchhof,* C. 1932 I 1838; *Karstens,* C. 1933 I 3012; French Pat. 41,880 [1932], addition to French Pat. 725,700; French Pat. 785,257 [1935]).

The action of hydrogen halides gives *rubber hydrohalides* of the approximate constitution $(C_5H_8 \cdot HHal)_x$ (*Weber,* Ber. **33**, 779). Removal of HCl from the hydrochloride gives α-iso-rubber, which differs from natural rubber in the positions of its double bonds, as is shown by ozonolysis (see p. 342) (*Harries,* Ber. **46**, 733). For syntheses of methyl- and ethyl-hydro-rubber, see *Staudinger* and *Widmer,* Helv. **7**, 842. Treatment of the hydrochloride or the hydrobromide with Zn dust and acetic acid does not give hydro-rubber (see below), but ring closure takes place with loss of HCl or HBr, as in the formation of α- and β-cyclogeraniolene from 2:6-dimethyl-2:6-dibromoheptane. The cyclo-rubber so obtained is very similar to that prepared by the heat treatment of rubber (see above) (*Staudinger* and *Bondy,* Ann. **468**, 12). For the hydriodide, see *Harries,* Ber. **46**, 737; *Hinrichsen, Quensell* and *Kindscher, ib.* 1283.

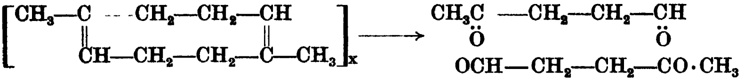
The action of N_2O_3 on rubber gives as the primary product *nitrosite* A $(C_{10}H_{16}N_2O_3)_x$, which is insoluble in organic solvents and alkali; the end-product is *nitrosite* C $(C_{10}H_{15}N_3O_7)_2$, decomp. 158–160°, a yellow powder soluble in ethyl acetate and acetone, which has been recommended for the quantitative estimation of rubber in mixtures (*Harries,* Ber. **35**, 4429; **36**, 1939); it is not a derivative of rubber, but of a degradation product. For the action of N_2O_4 on rubber, see *Emden,* Ber. **58**, 2524. The reaction of rubber with nitrosobenzene gives $(C_{11}H_{11}ON)_x$, decomp. 135–140° (*Pummerer* and *Gundel,* Ber. **61**, 1591; *Staudinger* and *Joseph,* Ber. **63**, 2888). With tetranitromethane rubber solutions give at first the characteristic yellow colour of an unsaturated substance; a colourless compound then separates which contains one $C(NO_2)_4$ for approx. 5 C_5H_8-groups (*Pummerer* and *Pahl,* Ber. **60**, 2159). For the effect of S_2Cl_2 on rubber, see under vulcanisation (p. 339).

The **hydrogenation** of rubber is of particular significance for the determination of the structure and the size of the molecule (see p. 344), and hence has been frequently investigated. Vigorous hydrogenation (270°, 100 atm.) or the reduction of a dilute solution of rubber give the same saturated *hydro-rubber,* $(C_5H_{10})_x$ ("*polyprane*") (*Staudinger,* Ber. **57**, 1203; *Staudinger* and *Schaal,* Helv. **13**, 1355), which is stable to bromine and permanganate; the pyrogenic decomposition of hydro-rubber at 350—400° yields a series of ethylenic hydrocarbons, the lowest of which is asym. methylethyl-ethylene and the highest a compound $C_{50}H_{100}$ (*Pummerer, Nielsen* and *Gündel,* Ber. **60**, 2167). More recent experiments carried out with rigorous exclusion of oxygen, in methylcyclohexane with Ni and H_2 at 100—130° under 100 atm., give a different hydro-rubber $(C_5H_{10})_x$; this is exactly like rubber in elasticity and appearance, but behaves as a saturated hydrocarbon towards bromine and tetranitromethane and, unlike rubber, is unaltered by a short exposure to air. Determination of the molecular weight by the viscosity method gives the same value as for the original rubber, and hence this hydro-rubber contains the carbon skeleton of rubber unchanged (*Staudinger* and *Leupold,* Ber. **67**, 304).

Purified rubber is **oxidised** much more readily than the natural material; it is attacked even by air, particularly under the influence of light. Various substances can act as accelerators (nitrosodimethylaniline, Cu and Mn salts) or as stabilisers (antioxidants, see p. 339). By the action of O_2 and of perbenzoic acid on dilute rubber solution, one atom of O is taken up per C_5H_8-

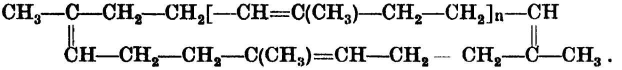
group, with the formation of a white, viscous, insoluble substance $(C_5H_8O)_x$ (*Pummerer* and *Burkard*, Ber. **55**, 3465).

By the **action of ozone** upon rubber, *Harries* obtained an *ozonide* $(C_5H_8O_3)_x$ and an "*oxozonide*" $(C_5H_8O_4)_x$, according to the conditions; both of these decompose to yield laevulinic aldehyde, laevulinic acid and laevulinic aldehyde peroxide (Ber. 38, 1195). On the basis of these results *Harries* suggested that rubber was a polymer of 1:5-dimethyl-cyclo-octadiene-1:5:



$$\left[\begin{array}{l} CH_3—C—CH_2—CH_2—CH \\ \quad\ \| \qquad\qquad\qquad\quad \| \\ \quad CH—CH_2—CH_2—C—CH_3 \end{array}\right]_x \longrightarrow \begin{array}{l} CH_3C—CH_2—CH_2—CH \\ \quad \ddot{O} \qquad\qquad\qquad \ddot{O} \\ \quad OCH—CH_2—CH_2—CO\cdot CH_3 \end{array}$$

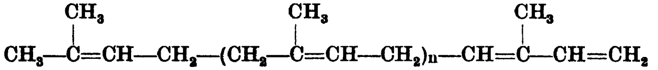
but he abandoned this formula, because ozonolysis of α-isorubber gave degradation products of higher molecular weight. *α-Iso-rubber*, obtained from rubber hydrochloride (see above) and pyridine, differs from rubber in its molecular size and in the positions of its double bonds (*Harries*, Ber. **46**, 733). *Harries* obtained the following by ozonolysis: laevulinic aldehyde, diacetylpropane, methylcyclohexenone (formed from diacetylpropane), a *triketone*, $C_{11}H_{18}O_3$, m.p. 93–94°, and a *tetraketone*, $C_{15}H_{24}O_4$, m.p. 123°. The formation of the two latter excluded the presence of an eight-membered ring, and *Harries* then (1914) proposed as the unit of the rubber molecule a poly-membered ring composed of four or five C_5H_8-residues, e.g.



$$\begin{array}{l} CH_3—C—CH_2—CH_2[—CH{=}C(CH_3)—CH_2—CH_2]_n—CH \\ \qquad\ \| \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad \| \\ \qquad CH—CH_2—CH_2—C(CH_3){=}CH—CH_2—CH_2—C—CH_3\,. \end{array}$$

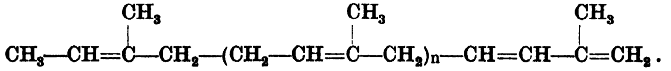
Weber, on the other hand, was the first to propose a chain-formula for rubber (Ber. **33**, 786), and this formulation was later supported by the many experiments of *Staudinger*. A long-chain compound which on ozonolysis will give laevulinic aldehyde as the main product (*Harries* obtained 60% of laevulinic derivatives, *Pummerer* obtained 90% [Ber. **64**, 804, 809]) can be built up in the following ways:

I.



$$CH_3—\overset{\displaystyle CH_3}{\overset{|}{C}}{=}CH—CH_2—(CH_2—\overset{\displaystyle CH_3}{\overset{|}{C}}{=}CH—CH_2)_n—CH{=}\overset{\displaystyle CH_3}{\overset{|}{C}}—CH{=}CH_2$$

II.

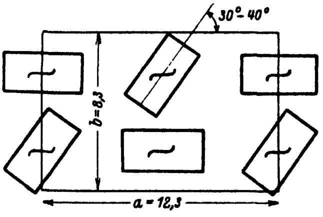


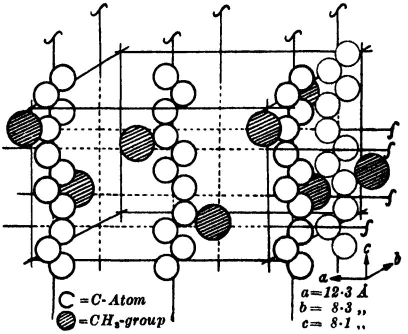
$$CH_3—CH{=}\overset{\displaystyle CH_3}{\overset{|}{C}}—CH_2—(CH_2—CH{=}\overset{\displaystyle CH_3}{\overset{|}{C}}—CH_2)_n—CH{=}CH—\overset{\displaystyle CH_3}{\overset{|}{C}}{=}CH_2\,.$$

The end-members of the first of these chains will give on ozonolysis acetone, malonic dialdehyde, methylglyoxal and formaldehyde; the second will give acetaldehyde, acetoacetic aldehyde, methylglyoxal and formaldehyde. Because of the absence of methylglyoxal in the ozonolysis product, *Harries* preferred the ring-structure, but *Pummerer* and *Matthaeus* succeeded in finding small quantities of methylglyoxal and acetaldehyde (together with acetic acid, succinic acid and CO_2) which indicates that the chain-formula II is correct (see also *Pummerer*, *Matthaeus* and *Socias-Vinals*, Ber. **69**, 170).

The size of the rubber molecule. — From the reactions of rubber, and particularly from its degradation products with ozone, it is clear that the molecule consists of a number of C_5H_8-groups (isoprene-residues) in a regular arrangement. There are two contradictory views as to the actual number. According to one, rubber possesses a basic molecule composed of few isoprene units; these basic molecules are united by secondary valencies which arise from the double bonds, to form the rubber particles, which now possess the characteristic properties of rubber, elasticity, tensile strength and formation of colloidal solutions. In such a solution the colloidal unit is a micelle which is composed of an aggregate of the basic molecules and has taken up more or less of the solvent, i.e. has become solvated. According to the other view, rubber is composed of macro-molecules formed of a very large number of isoprene units; these macro-molecules are the colloidal particles in solution, and rubber must be regarded as a eucolloid (*Staudinger*). The basic molecule or the macro-molecule can be a chain or a ring. No quantitative information as to the size of the molecule has yet been obtained from chemical methods of molecular weight determination (e.g. preparation of halogen derivatives, ozonolysis, etc.). The formation of methylglyoxal (see above) in the ozonolysis, however, is in favour of the chain-formula, and the earlier work on the X-ray diagram of stretched rubber by *K. H. Meyer* and *H. Mark*[1] showed clearly the presence of long chains of isoprene residues (Ber. **61**, 1942; *Meyer* and *Lothmar*, Mo. **69**, 115).

Rubber gives a fibre diagram, which is interpreted in the following way: a rhombic elementary cell with the dimensions a = 12·3 Å, b = 8·3 Å, c = 8·1 Å, with the c-axis in the direction of the fibre axis, contains four units each of two isoprene residues; the primary valencies extend outside the elementary cell, so that a long chain of primary valencies is present in the direction of the axis of the fibre. The length of these primary valency chains was estimated by *Meyer* and *Mark* to be from $(C_5H_8)_{75}$ to $(C_5H_8)_{150}$. If the space occupied by 4 units of 2 isoprene residues each is calculated from the known dimensions of the C—C and C=C bonds, the result agrees with that found experimentally, provided that the two CH_2-groups carrying the double bonds are in the cis-position to each other, and that each isoprene molecule is followed by one inclined at 180° to it; this is shown in the following diagrams, which also show the relative positions of the primary valency chains:





In an attempt to decide whether rubber is present in solution as a micelle or as a macro-molecule, molecular weight determinations in solution have been carried out. Only average values can be obtained, since the differences in solubility of various rubber preparations show that a mixture of several large molecular aggregates or macro-molecules is present (see p. 339). The following methods have been used, the results from which are not always in agreement with each other: the cryoscopic method (*Pummerer*, *Andriessen* and *Gündel*, Ber. **62**, 2628; see also *Signer*, Ann. **478**, 246); the osmotic pressure method (*Meyer* and *Mark*, Ber. **61**, 1946; *Schulz*, Z. physikal. Chem. A. **176**, 317); and the viscometric method[1], etc. (e.g. *Krüger*, C. 1928 I 2546; *Staudinger*, Z. angew. Chem. **49**, 801).

---

[1] Der Aufbau der hochpolymeren organischen Naturstoffe, p. 189, Leipzig 1930.

In the latter method it has been concluded, from the study of a large mass of facts collected in the investigation of synthetic polymers (chiefly polystyrenes, which serve as a model for rubber, poly-vinyl acetates and poly-ethylene oxides), that the viscosity is a simple function of the chain length of the dissolved substance, provided that the molecules are rod-shaped and only surrounded by a monomolecular layer of solvent, i.e. are not associated, and also that they are in very dilute solution. The following relationship then holds: $\frac{\eta_{sp}}{c_g} = K_m \cdot M$; η_{sp} = the rise in viscosity which the solute causes when dissolved in the solvent; c_g = the concentration of the solute in moles of fundamental unit per litre (for rubber, C_5H_8, i.e. 68); K_m is a characteristic constant for each polymeric homologous series, and is derived from measurements on "hemicolloids" of the same series, the molecular weight of which can be determined by the cryoscopic method. The hemicolloids can be obtained either by polymerisation of the fundamental substance (as in the polystyrenes) or by degradation of the macro-molecule (as in rubber and balata). M is the molecular weight. For the validity of this rule cf. *Staudinger*, Ber. **67**, 92; *Sakurada*, *ib.* 1045; *Mark*, C. 1934 II 1112; *Staudinger* and *Bauer*, Helv. **17**, 863; *Staudinger*, *ib.* 866; Ber. **69**, 1168. The following values have been obtained for M (*Staudinger* and *Leupold*, Ber. **67**, 304; cf. *Staudinger* and *Heuer*, *ib.* 1159, 1164):

Hevea-rubber, not purified	180,000,	i.e. c. $(C_5H_8)_{2600}$
Difficultly soluble gel-rubber	140,000,	i.e. c. $(C_5H_8)_{2000}$
Purified rubber, soluble in benzene	88,000,	i.e. c. $(C_5H_8)_{1300}$
Purified rubber, soluble in ether	64,000,	i.e. c. $(C_5H_8)_{930}$
Macerated rubber	20,000,	i.e. c. $(C_5H_8)_{300}$

These particles might still be considered as molecular aggregates held together by the secondary valencies of the double bonds, if the hydrogenation of rubber (see above) had not given a hydro-rubber of the same viscosity and hence with the same molecular weight as the original rubber. Since the partial valencies which might be held responsible for holding together the aggregates of small molecules vanish with the saturation of the double bonds, the conclusion is justified that, in fact, the colloidal particles of rubber are macro-molecules of various sizes, i.e. a mixture of homologous polymeric hydrocarbons $(C_5H_8)_x$, and further that the specific properties of rubber (elasticity, tensile strength, etc.) are not derived from the double bonds, but from the nature of the molecules as long "rigid, elastic fibres" (*Staudinger* and *Leupold*, Ber. **67**, 304, 307; *Staudinger* and *Mojen*, C. 1936 II 3649).

The synthesis of rubber and artificial rubbers. — Since the formula of rubber represents it as a polymer of isoprene (*polyprene*) and since isoprene is obtained from rubber by distillation, attempts have been made to build up rubber from isoprene, and were undertaken before its molecular size and structure were clear. The observation that isoprene can be converted into a rubbery mass was made by *Tilden* many years ago. Systematic search for a substance which, like rubber, gives laevulinic derivatives on ozonolysis, and which can be vulcanised to give elastic products, began in 1904 as a result of the work of *Harries*.

---

[1] *Staudinger*, Die hochmolekularen organischen Verbindungen Kautschuk und Cellulose. Berlin 1932.

The following methods have been found:

(1) *Heat polymerisation* (*F. Hofmann*, 1909); isoprene is heated for 8 days at 120–200°, or for a longer time at a lower temperature.

(2) *Heat polymerisation in acetic acid solution* in a closed vessel at 100° (*Harries*, 1910).

(3) *Sodium polymerisation* (*Harries*, and *Matthews* and *Strange*, 1910); isoprene is heated for a long time at 60° with Na.

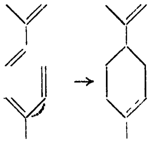
(4) *Sodium-carbon dioxide polymerisation* (*Holt*, 1914); isoprene is polymerised Na in the presence of CO_2.

Several other methods of polymerisation were worked out later, such as the ozonide method.

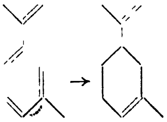
The rubbers obtained by methods (1), (2) and (4) are very similar to natural rubber in their behaviour to bromine and ozone, which points to considerable similarities in structure. The average chain length is however different, and no fibre diagram is obtained from the stretched material. The vulcanised products are inferior to those from natural rubber. The "sodium-rubber" prepared by method (3) is quite different from natural rubber and from the other three synthetic polyprenes. Its ozonolysis yields mainly products of high molecular weight.

Detailed investigation of the polymerisation of two molecules of isoprene has been very important for the understanding of the chemical processes which take place in these polyprene syntheses.

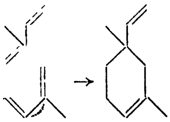
Isoprene, which takes up H_2 and Br_2 in the 1:4-positions (*Midgley jun.* and *Henne*, Am. 51, 1294), also condenses with a second molecule of isoprene in the 1:4-positions (a special case of the diene-synthesis), with the formation of the following cyclic products (*Wagner-Jauregg*, Ann. 488, 176):



I. *Dipentene*
(p. 201) (at
higher temperatures)

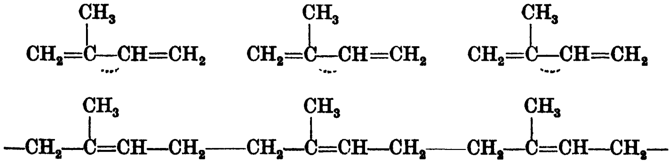


II. *Diprene*
(p. 214) (at
lower temperatures



III. Hydrocarbon of
Lebedev (constitution
not proved)

Rubber is the only aliphatic polymer of isoprene, since 1:4-addition with chain-formation does not cease after the condensation of two molecules together, but can lead to products of high molecular weight:

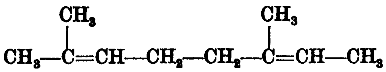


$$CH_2{=}\overset{\displaystyle CH_3}{\overset{|}{C}}{-}CH{=}CH_2 \qquad CH_2{=}\overset{\displaystyle CH_3}{\overset{|}{C}}{-}CH{=}CH_2 \qquad CH_2{=}\overset{\displaystyle CH_3}{\overset{|}{C}}{-}CH{=}CH_2$$

$$-CH_2{-}\overset{\displaystyle CH_3}{\overset{|}{C}}{=}CH{-}CH_2{-\!\!-}CH_2{-}\overset{\displaystyle CH_3}{\overset{|}{C}}{=}CH{-}CH_2{-\!\!-}CH_2{-}\overset{\displaystyle CH_3}{\overset{|}{C}}{=}CH{-}CH_2{-}$$

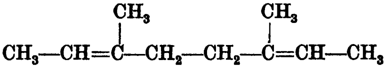
The intermediate product composed of two molecules of isoprene can, however, be detected:

(1) by reduction; when isoprene is treated with K and alcohol it gives 2:6-dimethyl-2:6-octadiene:

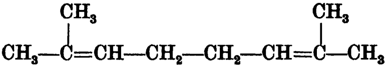


$$CH_3-\underset{}{\overset{\begin{array}{c}CH_3\\|\end{array}}{C}}=CH-CH_2-CH_2-\overset{\begin{array}{c}CH_3\\|\end{array}}{C}=CH-CH_3$$

In addition 3:6- and 2:7-dimethyl-2:6-octadiene are formed (*Midgley jun.* and *Henne*, Am. **51**, 1294); these take no part in the formation of normal rubber:

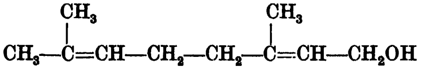


$$CH_3-CH=\overset{\begin{array}{c}CH_3\\|\end{array}}{C}-CH_2-CH_2-\overset{\begin{array}{c}CH_3\\|\end{array}}{C}=CH-CH_3$$



$$CH_3-\overset{\begin{array}{c}CH_3\\|\end{array}}{C}=CH-CH_2-CH_2-CH=\overset{\begin{array}{c}CH_3\\|\end{array}}{C}-CH_3$$

(2) with acetic and sulphuric acids (0·3%) the acetate of geraniol (p. 201) is formed:



$$CH_3-\overset{\begin{array}{c}CH_3\\|\end{array}}{C}=CH-CH_2-CH_2-\overset{\begin{array}{c}CH_3\\|\end{array}}{C}=CH-CH_2OH$$

Other products are aliphatic primary monoterpene alcohols of unknown constitution, and cyclic mono- and sesqui-terpene hydrocarbons and alcohols (*Wagner-Jauregg*, Ann. **496**, 52).

The different course of reaction in the polymerisation of isoprene with *alkali metals* is explained by the fact that the metal-alkyl butadiene first formed can undergo allyl tautomerism thus:

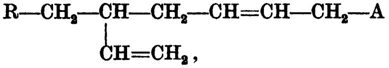
$$R-CH_2-CH=CH-CH_2-A \rightleftarrows R-CH_2-CH(A)-CH=CH_2$$

(A represents alkali metal)

Addition of another molecule of butadiene can take place in the 1:4- as well as in the 1:2-position, to give

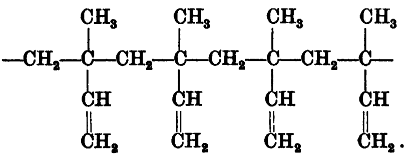
$$R-CH_2-CH=CH-CH_2-CH_2-CH=CH-CH_2-A$$

and



$$R-CH_2-\underset{\begin{array}{c}|\\CH=CH_2\end{array}}{CH}-CH_2-CH=CH-CH_2-A,$$

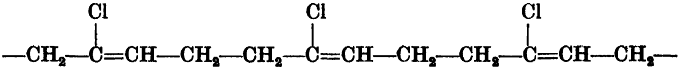
which can then again react in two forms (*Ziegler*, *Dersch* and *Wollthan*, Ann. **511**, 13). From the results which have been observed in the interaction of Li-butyl with butadiene, it can be assumed that the structure of sodium-rubber (prepared by process 3, p. 345) is as follows, and arises from a series of additions in the 1:2 position:



$$-CH_2-\underset{\begin{array}{c}|\\CH\\\|\\CH_2\end{array}}{\overset{\begin{array}{c}CH_3\\|\end{array}}{C}}-CH_2-\underset{\begin{array}{c}|\\CH\\\|\\CH_2\end{array}}{\overset{\begin{array}{c}CH_3\\|\end{array}}{C}}-CH_2-\underset{\begin{array}{c}|\\CH\\\|\\CH_2\end{array}}{\overset{\begin{array}{c}CH_3\\|\end{array}}{C}}-CH_2-\underset{\begin{array}{c}|\\CH\\\|\\CH_2\end{array}}{\overset{\begin{array}{c}CH_3\\|\end{array}}{C}}-\,.$$

The presence of CO_2 during the sodium polymerisation of isoprene (process 4, p. 345) displaces the equilibrium given above to the left and leads to 1:4-addition.

Lower and higher homologues of isoprene rubber have been obtained by the application of various methods of polymerisation to butadiene, which gives *butadiene-rubber* (*nor-rubber*; "*buna*"; for its properties see *Koch*, C. 1936 II 3213; *Hofmann*, Naturwiss. **24**, 423; *Konrad*, Angew. Chem. **49**, 799), and to 2:3-dimethyl-butadiene-1:3 (I, 117), which gives *methyl-rubber.* Because dimethyl-butadiene is relatively easy to obtain, methyl-rubber attained considerable importance in Germany during the Great War. Its properties, however, are inferior to those of the natural product, although recent experiments with butadiene-rubber have given very much more favourable results. 2-Chlorobutadiene-1:3, *chloroprene* (from vinylacetylene [I, 117] and HCl, followed by rearrangement) can also be polymerised to various rubber-like products (*Carothers*, *Williams*, *Collins* and *Kirby*, Am. **53**, 4203; *Carothers* and *Coffmann*, Am. **54**, 4071; Brit. Pat. 387,363 [1931]; *Klebansky* and *Vassiljeva*, J. pr. **144**, 251). The μ-polymer, *chloroprene rubber*, is superior to natural rubber in that it is more resistant to oil and benzene and less porous to gases. In contrast to isoprene-rubber, it gives a fibre diagram when stretched (*Garbsch* and *Susich*, C. 1933 I 3132). Ozonolysis gives succinic acid (*Klebansky* and *Vassiljeva*, J. pr. **144**, 251; C. 1936 II 1895), which is additional evidence for the formula:



$$-CH_2-\overset{\displaystyle Cl}{\overset{|}{C}}=CH-CH_2-CH_2-\overset{\displaystyle Cl}{\overset{|}{C}}=CH-CH_2-CH_2-\overset{\displaystyle Cl}{\overset{|}{C}}=CH-CH_2-$$

Two substances closely related to rubber, **guttapercha** and **balata**, $(C_5H_8)x$, also are found in the milky sap of tropical trees (*Palaquium Gutta* and *oblongifolium*, and *Mimusops Balata*). Their crystalline constituents, white spherulites which become transparent and isotropic at 60—62°, and melt above 90°, are identical, as is shown by their X-ray diagrams (*Hauser* and *Susich*, C. 1931 II 3051; cf., however, their behaviour towards thioglycollic acid, *Holmberg*, Ber. **65**, 1350). On distillation they give isoprene, and irradiation causes polymerisation as with rubber (*Pummerer* and *Kehlen*, Ber. **66**, 1120). For cyclo-guttapercha, see *Staudinger* and *Bondy*, Ann. **468**, 10. Balata and guttapercha differ from rubber in their smaller elasticity, and by the fact that they become soft and plastic when warmed in water. *Staudinger*[1] allots to balata a constitution similar to that of rubber, but with a cis-position to the two methylene groups adjacent to the double bonds, whilst a trans-position is given in rubber, but *Meyer* and *Mark* give the reverse configuration on the basis of the X-ray diagrams (Book [footnote to p. 343] p. 204). From viscometric measurements *Staudinger* finds an average molecular weight of 40,000 to 50,000. *Hydrobalata*, $(C_5H_{10})x$, obtained by hydrogenation with complete exclusion of oxygen, is a tough, amorphous mass of low elasticity, rather like rubber, which, in contrast to balata, is very stable to oxidation (*Staudinger* and *Leupold*, Ber. **67**, 304). Guttapercha and balata are used technically as insulating materials, e.g. for cables (*Dean*, C. 1933 I 3636). For the formation of monocyclo-guttapercha and monocyclo-balata from the hydrochlorides with Zn dust and alcoholic potash, see *Hardie* and *Mair*, J. **1935**, 1239, 1242.

A series of naturally occurring polycyclic compounds with one or more double bonds and alcoholic or acidic groups are closely related to the polyterpenes. These are the resin acids (see below) and the sapogenins, the glycosides of which occur as saponins in various plants (soapwort, horse chestnut, etc.). Several of these sapogenins are converted by dehydrogenation with Se into 1:2:7-trimethylnaphthalene (sapotalene, see pp. 338 and 513 *et seq.*). These compounds, which are closely related to the polyterpenes, have been designated "polyterpenoids" (*Ruzicka*, *Brungger*, *Egli*, *Ehmann* and *Goldberg*, Helv. **15**, 1501). The carotenoids also (lycopin, carotene, xanthophyll etc.) are related to the polyterpenes, for they too are built up from a series of isoprene units.

Resins[2]

The resins are closely related to the terpenes, and occur with them in plant secretions. Naturally occurring solutions of them in essential oils and turpentine oils are known as balsams or gums; resins can be obtained from them by distilling off the volatile constituents in steam or in vacuo. They are solid, amorphous and usually glassy substances; their solutions in alcohol, ether, turpentine oils, etc., are used as industrial varnishes.

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[1] cf. Book (footnote on p. 343), p. 404.

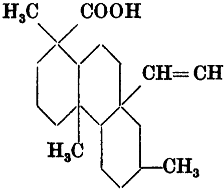
[2] *H. Wolff*, Die natürlichen Harze. Stuttgart 1928; *A. Tschirch* and *E. Stock*, Die Harze. 3rd ed. Berlin 1933; *R. D. Haworth*, Natural Resins, Ann. Rep. Chem. Soc. **33** (1936), 266.

Most natural resins appear to be mixtures of various characteristic acids, which are known as the resin acids. They are soluble in alkali to give resin-soaps, from which the resin acids are again precipitated by acids.

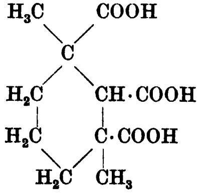
The resin acids which occur in the balsams from various species of *Pinus* have the formula $C_{20}H_{30}O_2$; some of them are very sensitive to heat, mineral acids and the oxygen of the air, and they crystallise with one another in isomorphous mixtures; these properties make their isolation and characterisation very difficult. According to *Dupont*, they can be grouped as follows:

A. **Terebenthic acids,** the constituents of the various kinds of galipot.

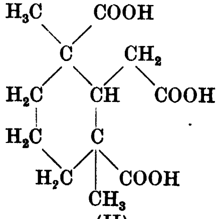
(1) **Pimaric acids: Dextropimaric acid,** *α-pimaric acid,* is found in turpentine of Bordeaux, from *Pinus sylvestris* and *Pinus laricio,* and in American turpentine; m.p. 210–211°, $[\alpha]_{\text{Hg yellow}} + 75° 4'$. It is very stable towards heat and acids, and can be obtained almost unchanged from its hydrochloride with quinoline (*Ruzicka* and *Balas,* Ann. **460**, 203). It contains two double bonds, which have different reactivities, as shown by the addition of oxygen with perbenzoic acid, and of H_2 with a very reactive catalyst (*Ruzicka, Huyser* and *Seidel,* Rec. **47**, 363). Dehydrogenation with sulphur gives $C_{16}H_{14}$, 1:7-dimethylphenanthrene, *pimanthrene,* m.p. 86° (*picrate* m.p. 131–132°), formed by the loss of the carboxyl, a methyl, and the vinyl group (*Haworth, Letsky* and *Mavin,* J. **1932**, 1784). The *methyl ester* of *d*-pimaric acid has m.p. 69°. *Homopimanthrene,* 7-methyl-1-ethylphenanthrene, m.p. 81° (*picrate* m.p. 115–116°), is formed from dextropimaric acid in the same way as homoretene is from abietic acid (p. 349) (synthesis: *Haworth,* J. **1932**, 2717). Oxidation with $KMnO_4$ gives *dihydroxy-dihydro-dextropimaric acid,* $C_{20}H_{30}O_2(OH)_2$ (*Balas,* C. 1929 I 2530), which is converted by CrO_3 into the *dicarboxylic acid* $C_{19}H_{28}O_4$, m.p. 260–261°; this has one C-atom less and contains one double bond. Energetic oxidation with nitric acid gives two acids; $C_{11}H_{16}O_6$ (I), m.p. 218–219°, and $C_{12}H_{18}O_6$ (II), m.p. 212–213°, which can be obtained from abietic acid (see below) in the same manner. Dextropimaric acid probably has formula (III) (*Ruzicka, de Graaff* and *Müller,* Helv. **15**, 1300; *Haworth,* J. **1932**, 2717):



(III)



(I)



(II)

There is one double bond in the ring-system, its position being uncertain. For the action of perbenzoic acid upon dextro-pimaric acid, see *Ruzicka* and *Frank,* Helv. **15**, 1294.

Laevopimaric acid, *β-pimaric acid, sapietic acid,* is not, as its name would imply, the optical antimer of α-pimaric acid. It is present in turpentine of Bordeaux, from *Pinus laricio,* and in the resin from *Picea excelsa* (*Dupont,*

C. r. **172**, 1373); m.p. 150–152°, $[\alpha]_{\text{Hg yellow}}$ — 282·4°. When boiled in acetic acid solution it gives abietic acid; catalytic reduction shows the presence of two double bonds (*Ruzicka, Balas* and *Vilim*, Helv. **7**, 458). Treatment of laevopimaric acid with maleic anhydride gives the same adduct as that obtained from abietic acid (*Bacon* and *Ruzicka*, Chem. and Ind. **55** (1936), 546; see also *Wienhaus* and *Sandermann*, Ber. **69**, 2202).

(2) **Sapinic acids** are easily oxidised, and very unstable towards heat; they are converted, via various intermediates, into abietic acid. For the most part they appear to be mixtures of dextropimaric and laevopimaric acids with a "proabietic acid" (*Kraft*, Ann. **524**, 1). Several acids have been allotted to this group, but it is uncertain whether they are single compounds or mixtures (*Nordstrom*, J. pr. **121**, 204).

α-Aleppic acid, m.p. 148°, $[\alpha]_{\text{Hg yellow}}$ — 66° 2′, is found in galipot from *Pinus halepensis* and *Pinus laricio.*

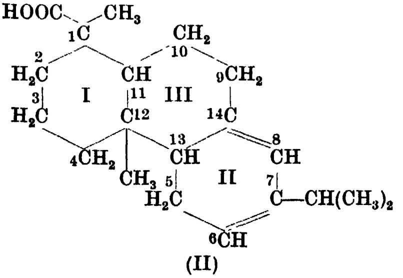
Laricinic acid, m.p. 146–147°, $[\alpha]_D^{20}$ — 48·5°, is obtained from Venetian turpentine (*Trost*, Ann. chim. appl. **25**, 496).

Pineinic acid, m.p. 119–120°, $[\alpha]_{\text{Hg yellow}}$ — 113° 3′, is found in the galipot from *Pinus pinea* (*Dupont* and *Dubourg*, Bull. **39** (1926), 1029).

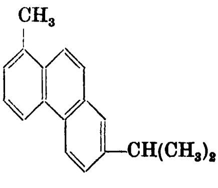
β-Sapinic acid, m.p. 140°, $[\alpha]_{\text{Hg yellow}}$ — 161°, from the galipot of *Pinus maritima* (*id.*, C. 1928 II 1434), and **sapinic acid** from American pine resin, m.p. 141–144°, have been shown to be mixtures of dextropimaric and laevopimaric acids and their rearrangement products (*Kraft*, Ann. **520**, 133).

B. **Colophanic acids,** products of the rearrangement of terebinthic acids by heat (*colophonic acids* according to *Aschan*) and by mineral acids (*sylvinic acids* according to *Aschan*).

The most fully investigated compound of this series is **abietic acid,** m.p. 173°, $[\alpha]_{\text{Hg yellow}}$ approx. — 100° (*Schulz*, Chem. Ztg. **41**, 666). It contains two double bonds, as is shown by its oxidation to *tetrahydroxy-abietic acid*, $C_{19}H_{29}(OH)_4COOH$, m.p. 246–247° (*Levy*, Ber. **42**, 4305; **61**, 616), and by the catalytic hydrogenation to tetrahydro-abietic acids. Abietic acid must therefore be tricyclic, and since on dehydrogenation it yields retene, 1-methyl-7-isopropyl-phenanthrene (I), m.p. 98–99° (*picrate* m.p. 123–124°) (*Vesterberg*, Ber. **36**, 4200; *Diels* and *Karstens*, Ber. **60**, 2323; synthesis, *Bardhan* and *Sengupta*, J. **1932**, 2798), it must have a hydrogenated phenanthrene skeleton. In the dehydrogenation, CO_2 and a methyl group are lost; this fact together with the lack of reactivity of the carboxyl group, the investigation of the acids obtained by oxidation, $C_{12}H_{18}O_6$ (II, p. 348) and $C_{11}H_{16}O_6$ (I, p. 348), and the principle that the molecule must be built up of isoprene units, has led to the formula (II) for abietic acid (*Vocke*, Ann. **497**, 247; *Ruzicka, Waldmann, Meier* and *Hosli*, Helv. **16**, 169; *Ruzicka* and *Waldmann*, *ib.* 842; see also *Vocke*, Ann. **508**, 11):



(II)



(I)

The position of the double bonds is not known with certainty; they were placed in the positions shown because with maleic anhydride an addition compound is formed, but this reaction does not take place below 130°, and the spectroscopic and refractivity data do not support conjugation of the double bonds (*Wienhaus*, *Ritter* and *Sandermann*, Ber. **69**, 2198). Abietic acid forms a *nitrosochloride*, m.p. 145°, a *nitrosite*, m.p. 77°, and an *acid Na salt*, 3 $C_{20}H_{30}O_2 + C_{19}H_{29}COONa$, m.p. 175° (*Dupont*, *Desalbres* and *Bernette*, Bull. **39** (1926), 488). For esters of abietic acid and their halogen halide addition products, see *Levy*, Ber. **64**, 2441. From abietic acid are derived: *abietene*, $C_{19}H_{30}$, formed by decarboxylation, and *abietin*, $C_{19}H_{28}$, formed from the acid chloride $C_{19}H_{29}COCl$ by distillation with loss of CO and HCl. Homoretene (previously known as *methylretene*), m.p. 79° (*picrate* m.p. 101–104°), is obtained by the following series of reactions: abietic ethyl ester $\xrightarrow[\text{alcohol}]{\text{Na}+}$ abietinol $\xrightarrow{PCl_5}$ homoabietin (formerly known as *methylabietin*) $\xrightarrow[\text{genation}]{\text{S-dehydro-}}$ homoretene. It has been shown to be 1-ethyl-7-isopropylphenanthrene (synthesis: *Haworth*, J. **1932**, 2717), and owes its formation to the migration of a carbon atom during the dehydration of the abietinol. Long heating converts abietic acid into the isomeric *pyroabietic acids*: *laevopyroabietic acid*, m.p. 194°, $[\alpha]^{20}_{D} - 15^{0}\ 2'$, and *dextropyroabietic acid*, m.p. 157°, $[\alpha]^{20}_{D} + 37{\cdot}5^{0}$ (*Fonrobert* and *Greth*, C. 1929 I 2642).

One dibasic acid, $C_{20}H_{30}O_4$, **agathic acid**, m.p. 204°, which is found in Kauri copal and hard and soft Manila copal, has, in contrast to the above acids, a bicyclic skeleton, and contains a hydrogenated naphthalene ring with two double bonds (*Ruzicka* and *Hosking*, Helv. **14**, 203). It can be converted into an isomer, **isoagathic acid**, which is a hydrogenated phenanthrene derivative. Both acids give pimanthrene (see above) on dehydrogenation (*Ruzicka* and *Hosking*, Helv. **13**, 1402). In addition agathic acid yields 1:2:5-trimethylnaphthalene (*agathalene*) (*Ruzicka* and *Ehmann*, Helv. **15**, 140), which is also obtained from tetracyclo-squalene.

Manila elemi resin contains a resin acid of high molecular weight, the monobasic hydroxy-acid **α-elemolic acid**, $C_{30}H_{48}O_3$, m.p. 226°. It is converted by oxidation into the ketonic acid $C_{30}H_{46}O_3$, **α-elemonic acid**, m.p. 274–275°, and dehydrogenation with Se yields 1:2:7-trimethylnaphthalene. α-Elemolic acid has two double bonds, one of which resists hydrogenation: *dihydro-α-elemolic acid*, $C_{30}H_{50}O_3$, m.p. 238° (*Ruzicka*, *Wakeman*, *Furter* and *Goldberg*, Helv. **15**, 1454; *Mladenović*, C. 1933 I 3724; *Lieb* and *Mladenović*, Mo. **62**, 232). Manila elemi resin contains also a tetracyclic ketonic acid with two double bonds, **δ-elemic acid** (*β*-elemonic acid), $C_{30}H_{46}O_3$, m.p. 220°; the *tetrahydro-acid*, $C_{30}H_{50}O_3$, has m.p. 244° (*oxime* m.p. 245°) (*Mladenović* and *Berkeš*, Mo. **67**, 36). Further the crude resin yields a *hydroxy-acid*, **γ-elemic acid**, $C_{30}H_{50}O_3$, m.p. 281° (*Lieb* and *Mladenović*, Mo. **58**, 59, 69); **β-elemic acid** seems to be a mixture of the α- and γ-acids and amyrin (*Mladenović*, C. 1933 I 3724).

For *boswellinic acid*, $C_{30}H_{48}O_3$, the resin acid of incense, a monohydroxy-triterpene acid, see p. 514.

Shellolic acid, $C_{15}H_{20}O_6$, m.p. 199·5–201° (*dimethyl ester* m.p. 149°), is a hydroaromatic dihydroxy-dicarboxylic acid obtained from shellac. Its *diphenylurethane*, $C_{31}H_{34}N_2O_8$, has m.p. 92–94°. Shellac is the purified commercial form of the lac exuded by various Indian species of *Ficus* as a result of the attacks of various insects. The pure resin can be decomposed by careful hydrolysis into aliphatic and hydroaromatic hydroxy-acids. It must be regarded as the mixed lactides of these acids, and it contains free COOH-groups. The decomposition product gives, besides shellolic acid, **aleuritinic acid**, $C_{16}H_{32}O_5$, 9:10:16-trihydroxy-palmitic acid; in contrast to shellolic acid this forms a sparingly soluble K salt; *methyl ester* m.p. 63–64°; *ethyl ester* m.p. 58°. Oxidation with $KMnO_4$ yields azelaic acid and heptanol-7-carboxylic acid, which is evidence for the following formula:

$$CH_2OH{\cdot}(CH_2)_5{\cdot}CHOH{\cdot}CHOH{\cdot}(CH_2)_7{\cdot}COOH$$

(*Harries* and *Nagel*, Ber. **55**, 3833; *Harries*, Ber. **56**, 1048; see also *Harries* and *Nagel*, C. 1924 II 1187; *Nagel*, C. 1931 II 557; *Nagel* and *Mertens*, Ber. **69**, 2050).

Amber, a fossil resin found on the coasts of the Baltic sea, is a mixture of various resin acids and esters; it can be separated by alcohol into a soluble part (30%) and an insoluble part (70%). By treatment of the soluble portion with other solvents (light petroleum, ether, etc.), the following compounds can be isolated: succinic acid, borneol, **succinoxy-abietic acid,** m.p. 124–126°, a hydroxy-acid **succinoabietinolic acid,** m.p. 164°, and an **alcohol,** m.p. 115°. When the portion insoluble in alcohol is treated with KOH, the products are succinic acid, a compound of m.p. 137°, and two indifferent substances (resenes) with decomp. points above 350°. Dehydrogenation of these with Se gives pimanthrene and a hydrocarbon $C_{13}H_{14}$, m.p. 28° (*picrate* m.p. 139·5°), of unknown composition (*Schmid* and *Erdös*, Ann. **508**, 269).

B. NATURAL PRODUCTS

In this section a large number of compounds found in the plant and animal kingdoms are dealt with. They are divided into a number of groups, the individual groups including either a series of compounds of similar molecular structure, as in the groups of the glycosides, the sterols and the bile acids, or of compounds with similar physical properties, such as the natural colouring matters, or with similar physiological or pharmacological effects, such as the tannins, pepper-like substances, non-nitrogenous poisons, vitamins and hormones. The various members of these groups are then treated separately, if their constituion is known. This method of classification, through possibly not logical, is the most practicable for the purposes of a text book. In addition to the compounds described here, other important groups of natural products are the carbohydrates and proteins treated in Vol. I., the terpenes discussed earlier in this volume and the plant alkaloids to be dealt with in Vol. IV. The compounds described in this section are divided into the following groups:

I. Glycosides
II. Tannins
III. The Active Principles of the Peppers
IV. Natural Colouring Matters
V. Non-nitrogenous Poisons
VI. Sterols and Bile Acids
VII. Vitamins
VIII. Hormones

I. GLYCOSIDES[1]

The glycosides include a large number of compounds chiefly found in the plant kingdom; under the influence of hydrolysing agents, e.g. by heating with water or dilute acids, or by the action of enzymes, they take up water and decompose to give one or more sugars and a sugar-free "aglycone"; the latter can belong to the most diverse kinds of chemical compounds. Sometimes in nature the position of the sugar component is taken by one of its higher oxidation products, e.g. glucuronic acid.

Laurent in 1852 was the first to place these substances into a special group, the "glucosamides". *Berthelot* later called them "saccharides". The detailed investigation of amygdalin by *Liebig* and *Wöhler* in 1837 formed the starting point for the study of the "glycosides".

The following table gives some of the important dates in the history of the discovery of the glycosides:

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[1] *E. F. Armstrong* and *K. F. Armstrong*, The Glycosides, London 1933; *J. van Rijn*, Die Glykoside, Berlin 1931; *Klein's* Handbuch der Pflanzenanalyse, Vol. III, Vienna 1932.

1815 Saponin (Grothus).
1822 Daphnin (Gmelin and Baer).
1827 Sinalbin (Henry and Corot).
1828 Digitalin (Dulong).
Hesperidin (Lebreton and Brandes).
1830 Salicin (Leroux; Buchner).
Amygdalin (Robiquet and Boutron).
1835 Phlorrhizin (de Koninck).
1840 Sinigrin (Robiquet and Bussy).
1841 Quercitrin (Bolly).
1852 Arbutin (Kawalier).
1861 Coniferin (Hartig).
1874 Phrenosin (Thudichum).
1875 Digitonin (Schmiedeberg).
1876 Vicin (Ritthausen).
Chitin (Ledderhose).
1894 Picein (Tanret).
1897 Linamarin (Jorissen and Hairs).
1901 Lotusin (Dunstan and Henry).
1903 Geranyl glucoside (Bourquelot).
1905 Gein (Bourquelot and Hérissey).
1909 Hydrangenol-glucoside (Asahina).
1913 Cyanin (Willstatter and Everest).
1914 Solanum glucoside (Oddo).
1919 Pharbitic acid (Asahina).
1920 Dryophanthin (Nierenstein).
1930 Chellolglucoside (Fantl).
1931 Daidzin (Walz).

The glycosides are isolated by extraction with water or organic solvents, which stops the hydrolysing action of the enzymes, followed by separation of the glycoside as some sparingly soluble derivative.

From observations on the occurrence of the glycosides in nature, the synthetic abilities of the various plant families can readily be seen; e.g. the *Cruciferae* give glycosides which are hydrolysed to compounds containing sulphur. On the other hand certain types of chemical compounds, e.g. the anthocyanins and saponins, seem to be synthesised very readily by plants of many kinds, and hence are widely distributed.

The glycosides appear to have various functions in the plants. Thus substances can be kept in reserve until needed, e.g. the hormones which exert a regulating stimulus on plant metabolism, or reserves of sugar. The hydrocyanic acid glucosides, the first products of nitrogen assimilation, may possibly represent an intermediate in the synthesis of protein; their formation may also be a means of rendering innocuous the HCN which is injurious to enzymatic cell processes. The addition of sugar molecules to the anthocyanidins acts as a protection of these colouring matters against oxidation. The glycosides of the bark or epidermis of plants possess an antiseptic action against insect pests.

The simplest glycosides were prepared by *E. Fischer* (1893) by the action of HCl on alcoholic solutions of sugars (I 694). Treatment of alcohols with the 1:2-oxides of sugars also leads to the corresponding glycosides (*Hickinbottom*, J. **1928**, 3140).

A method for the artificial preparation of glycosides due to *Michael* (1879) consists in the interaction of alcohols or phenols with acetochloro- or acetobromo-glucose (I 695) in alkaline alcoholic solution. Phenolglycosides may also be prepared catalytically from phenols and sugar acetates by the action of $ZnCl_2$ or p-toluene-sulphonic acid (*Helferich* and *Schmitz-Hillebrecht*, Ber. **66**, 378; *Helferich*, Brit. Pat. 394,195; *Helferich*, *Lang* and *Schmitz-Hillebrecht*, J. pr. **138**, 275; *Helferich* and *Peters*, ibid., 281).

The enzymatic synthesis of *Croft-Hill* (1898) has also become of very great importance (cf. *Ammon*, Z. angew. Chem. **45**, 357).

A consideration of various possible methods has shown that the glycosides are best classified according to the constitution of the aglycone.

(a) ALIPHATIC GLYCOSIDES

β-Methyl-d-glucoside, $C_6H_{11}O_5 \cdot OCH_3$, m.p. 110°, [α]$_D$ — 31·97°, is found in the leaves of *Dipsacaceae* (*Wattiez*, J. Pharm. Belg. **7**, 81; idem, Bull. Soc. Chim. Biol. **8** (1926), 501; J. Pharm. Belg. **11**, 597). For its synthesis see *Fischer*, Ber. **28**, 1151; *Koenigs* and *Knorr*, ibid. **34**, 965; *Fischer* and *Armstrong*, ibid., 2895).

α-Ethyl-galactoside, $C_6H_{11}O_5 \cdot OC_2H_5$, m.p. 140°, [α]$_D$ + 185·52°, has been isolated from lupins (*Fischer*, Ber. **47**, 456). It has been synthesised from galactose and alcohol with HCl (*Fischer* and *Armstrong*, Ber. **35**, 3155), or biochemically with yeast (*Hérissey* and *Aubry*, J. Pharm. Chim. (7) **9**, 327).

Gaultherioside, $C_{13}H_{24}O_{10}$, m.p. 185°, [α]$_D$ — 58°, obtained from fresh *Gaultheria procumbens*, gives *ethyl alcohol*, glucose and xylose on hydrolysis (*J. Rabate* and *S. Rabate*, Bull. Soc. Chim. Biol. **13** (1931), 604).

Floridoside, $C_9H_{18}O_8$, m.p. 87°, [α]$_D$ + 151°, a glycoside from the seaweed *Rhodymenia palmata* (*Florideae* group), is decomposed by hydrolysis with dilute sulphuric acid into galactose and *glycerol*; as it cannot be hydrolysed by emulsin, an α-glucosidic link is probably present, and the difficulty of oxidation with bromine indicates that it is attached to the secondary alcohol group (*Colin* and *Guéguen*, C. r. **190**, 653; **191**, 163 (1930); *Schmidt-Nielsen* and *Hammer*, C. 1933 I 3953).

A **glucoside** of **amyl alcohol** is contained in the roots of *Brauneria angustifolia* (*Colin* and *Guéguen*, C. r. **191**, 163).

Clavicepsin, $C_{18}H_{34}O_{16} \cdot H_2O$, m.p. 91°, anhydrous 198°, [α]$^{20}_D$ + 142·27°, is present to the extent of 1·5–2% in the ergot, *Claviceps purpurea* (*Secale cornutum*); hydrolysis yields *mannitol* $C_6H_{14}O_6$, m.p. 166°, [α]$_D$ + 22·5°, and 2 moles of glucose (*Zuco* and *Pasquero*, Gazz. **41** (1911), II 368).

Cetyl alcohol d-glucoside, $C_{22}H_{44}O_6$, m.p. 150°, [α]$_D$ — 22·02°, occurs in *sarsaparilla* root. For its synthesis from cetyl alcohol and acetobromoglucose, see *Fischer* and *Helferich*, Ann. **383**, 79; *Salway*, J. **103**, 1022.

Pharbitic acid, $C_{26}H_{48}O_{13}$, m.p. 156–162°, [α]$_D$ — 46·6°, is obtained from the seeds of *Pharbitis nil*. Acid hydrolysis gives ipurolic acid (3:11-*dihydroxymyristic acid*) $C_{14}H_{28}O_4$, glucose and rhamnose. The dihydroxy-acid can be reduced with HI to myristic acid $C_{14}H_{28}O_2$, m.p. 53·8°. As ipurolic acid is a β-hydroxy-acid, it can be dehydrated to an unsaturated monohydroxy-acid $C_{14}H_{26}O_3$; ozonolysis of this compound gives the ketonic acid $C_{12}H_{22}O_3$, m.p. 56° (8-butyryl-caprylic acid), and hydrogenation hydroxy-myristic acid $C_{14}H_{28}O_3$, m.p. 51°. The position of the second hydroxyl group follows from the oxidation of hydroxy-myristic acid to sebacic acid $C_{10}H_{18}O_4$, m.p. 133°, and butyric acid $C_4H_8O_2$. Direct oxidation of ipurolic acid gives 3:11-diketomyristic acid $C_{14}H_{24}O_4$, m.p. 69°, which can be decarboxylated to the corresponding diketone $C_{13}H_{24}O_2$, m.p. 49° (*Asahina* and *Shimidzu*, J. Pharm. Soc. Japan **479** (1922), 1; *Asahina* and *Nakanishi*, ibid. **520** (1925), 1).

Jalapic acid, $C_{34}H_{62}O_{18}$, m.p. 208°, is obtained from the resin of *Stipites Jalapae*, *Convolvulus orizabensis* and *Scammonia* (*Peyer* and *Rosenthal*, Apoth. Ztg. **44** (1929), 1329); it is used for its purgative and haemolytic action (*Heinrich*, Biochem. Z. **88**, 13), and paralyses the motor nerves and the parasympathetic system (*Hollander*, Compt. rend. Soc. Biol. **89** (1925), 1171). Hydrolysis decomposes it into jalapinolic acid (11-hydroxy-palmitic acid) $C_{16}H_{32}O_3$, m.p. 68°, and 3 mol. glucose (*Spirgatis*, Ann. **116**, 289; *Poleck*, Arch. Pharm. **232** (1894), 315; *Kromer*, J. pr. **57**, 448). The aglucone is shown to be a hydroxy-acid by the formation of an acetyl derivative, and on reduction with HI it is converted into palmitic acid $C_{16}H_{32}O_2$, m.p. 61·5°. Jalapinolic acid is oxidised by CrO_3 to a ketonic acid $C_{16}H_{30}O_3$, m.p. 74·5°; the position of the CO group in this acid, and hence of the OH in jalapinolic acid, is shown by the Beckmann rearrangement of the oxime to caproic acid, $C_6H_{12}O_2$, b.p. 200°, and 10-aminodecanoic acid $C_{10}H_{21}O_2N$, m.p. 185°, or undecandioic acid $C_{11}H_{20}O_4$, m.p. 110°; the constitution is also shown by the synthesis of 11-keto-hexadecanoic acid from $CH_3 \cdot (CH_2)_4 \cdot MgBr$ and $O{:}CH \cdot (CH_2)_9 \cdot COOCH_3$. Hence jalapinolic acid is 11-hydroxy-hexadecanoic acid (*Asahina* and *Yaoi*, J. Pharm. Soc. Japan **528** (1925), 5; *Davies* and *Adams*, Am. **50**, 1749).

Convolvulinic acid, $C_{52}H_{92}O_{32}\cdot 7H_2O$, m.p. 187°, $[\alpha]_D$ — 35·3°, obtained from the resin from *Convolvulus*, *Radix scammoniae*, and *Exogonium purga* (*Peyer* and *Rosenthal*, Apoth. Ztg. **44** (1929), 1329), is very similar to jalapic acid in physiological action. Treated with 10% oxalic acid it yields 4 mol. of glucose, 2 mol. of rhamnose, and convolvulinolic acid $C_{16}H_{32}O_4$, m.p. 84° (*Mayer*, Ann. **95**, 161; *Taverne*, Rec. **13**, 187; *Votoček*, Ber. **43**, 476). The latter has been identified as 3:12-dihydroxy-palmitic acid: the presence of two hydroxyl groups is shown by a Zerevitinov estimation, and HI reduces the acid to palmitic acid. The position of the hydroxyls was established by oxidative fission with CrO_3 into 2:11-diketo-pentadecane $C_{15}H_{28}O_2$, m.p. 64°, and CO_2, or acetic acid and 10-keto-tetradecanoic acid $C_{14}H_{26}O_3$, m.p. 69°; and further by the Beckmann rearrangement of the oxime of this ketonic acid into sebacic acid $C_{10}H_{18}O_4$, m.p. 133°, and n-butylamine $C_4H_{11}N$, or into n-valeric acid $C_5H_{10}O_2$, and 9-amino-nonanoic acid $C_9H_{19}O_2N$ (*Votoček* and *Valentin*, C. 1929 II 578; *Votoček* and *Prelog*, ibid. 579).

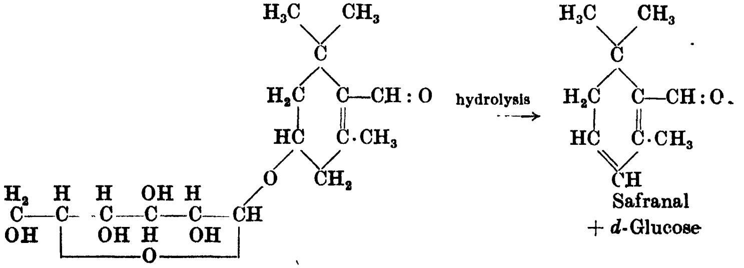
The **fats of bacteria** are composed mainly of ester-like compounds of polysaccharides with saturated and unsaturated fatty acids; e.g. the lipoids of the diphtheria bacteria yield not only *palmitic acid* $C_{16}H_{32}O_2$, but also palmitoleic acid $CH_3\cdot(CH_2)_5\cdot CH{:}CH\cdot(CH_2)_7\cdot COOH$ (methyl ester b.p. 110°/0·01 mm.) and an olefinic acid of higher molecular weight, diphtheric acid $C_{35}H_{68}O_2$, m.p. 36° (*Chargaff*, Z. physiol. Chem. **218**, 223).

For *tuberculo-stearic acid*, $C_{18}H_{36}O_2$, and *phthionic acid* $C_{26}H_{52}O_2$, which have branched chains and are obtained from tubercle bacilli, see p. 478.

(b) TERPENE GLYCOSIDES

Geranyl-glucoside, $C_{16}H_{28}O_6$, m.p. 58°, $[\alpha]_D$ — 37·25°, is found in *Pelargonium odoratum*; it has been synthesised from geraniol and *d*-glucose with emulsin (*Bourquelot* and *Bridel*, C. r. **157**, 72; idem, J. Pharm. Chim. (7) **8**, 204), and from geraniol and acetobromoglucose (*Fischer* and *Helferich*, Ann. **383**, 77).

Picrocrocin, $C_{16}H_{26}O_7$, m.p. 156°, $[\alpha]_D$ — 58° (tetracetate m.p. 143°; *tetracetate-semicarbazone* m.p. 105°), is a terpene glucoside obtained from various kinds of *Crocus* (*Safran aquila*, see *Winterstein* and *Teleczky*, Z. physiol. Chem. **120**, 141). Hydrolysis yields a monocyclic aldehyde with two double bonds, *safranal* (dehydro-β-cyclocitral), $C_{10}H_{14}O$ (p. 127), which is an oil with an odour of saffron, b.p. 185–205°, and glucose (*osazone* m.p. 205°) (see *Kayser*, Ber. **17**, 2228; *Winterstein* and *Teleczky*, Helv. **5**, 376; *Torelli*, C. 1923 IV 625; *Lutz*, Biochem. Z. **226**, 97). The carbon skeleton of the aglucone is clear from its conversion into β-cyclocitral (pp. 205 and 207) and into β-cyclogeranic acid; the conjugation of the double bonds with each other and with the CO group gives it a high molecular refraction. Since the molecular refraction shows that in the glucoside itself one double bond is conjugated with the CO group, the glucoside, formed by the addition of glucose to one double bond of safranal, has been given the following constitution (*Kuhn* and *Winterstein*, Ber. **67**, 344):



The rotation of picrocrocin indicates that it is a β-glucoside; its oxidation with lead tetracetate by the method of *Criegee* confirms the presence of the 1:5-oxide ring.

Picrocrocin is accompanied in nature by **crocin** $C_{18}H_{22}(COOC_{12}H_{21}O_{11})_2$, the digentiobiose ester of crocetin (see table, p. 413). The fact these two compounds occur together gives a valuable insight into the biochemistry of the carotenoids (see p. 417, and *Karrer* and *Salomon*, Helv. **16**, 643).

(c) AROMATIC GLYCOSIDES

Arbutin, $C_{12}H_{16}O_7 \cdot H_2O$, m.p. 142°, anhydrous m.p. 194°, $[\alpha]_D$ —62·16°, and **methylarbutin**, $C_{13}H_{18}O_7$, m.p. 160°, anhydrous 175°, $[\alpha]_D$ —63°, are found in the leaves of the bearberry (*Arctostaphylos* [*Arbutus*] *uva ursi*) and the pear (*Pyrus communis*) (*Schiff*, Ann. **206**, 159), and in the former is the cause of the dark colour of the leaves. Hydrolysis with emulsin or dilute acids gives *hydroquinone* or its methyl ether and glucose (*Strecker*, Ann. **107**, 228; *Moelwyn-Hughes*, Trans. Faraday Soc. **24** (1928), 309); it is also hydrolysed in the animal organism and eliminated in the urine as a conjugated sulphuric or glucuronic acid (*Bass*, Z. exp. Path. Therap. **10** (1911), 120; *Bourquelot* and *Fichtenholz*, C. r. **154**, 1106; J. Pharm. Chim. (7) **5**, 425). The two compounds have been synthesised from the alkali salts of hydroquinone or hydroquinone methyl ether and acetobromoglucose (*Michael*, Ber. **14**, 2098), and also by the action of the enzyme emulsin on the components (*Bayliss*, J. Physiol. **43**, 455; *Robertson* and *Walters*, J. **1930**, 2729). Arbutin is converted into methylarbutin with CH_3I and methyl alcoholic KOH (*Schiff*, Ber. **15**, 1841).

The **glucoside of benzyl alcohol** is said to occur in maize and in tolu balsam.

Salicin, $C_{13}H_{18}O_7$, m.p. 201°, $[\alpha]_D$ — 62·5°, has been obtained from the bark and the leaves of the willow (*Salix helix*) and of various species of poplar, and from the leaf-buds of *Spiraea ulmaria* (*Piria*, Ann. **96**, 378; *Moelwyn-Hughes*, Trans. Faraday Soc. **24** (1928), 309).

Salicin was discovered in 1830 almost simultaneously by *Leroux* (Ann. **1**, 43; **30**, 151) and by *Buchner* (Rep. Pharm. **29**, 411). Its nature and composition were established by *Piria* (Ann. **56**, 35) in a detailed investigation.

Salicin is hydrolysed by the enzymes ptyalin and emulsin into *saligenin* (salicyl alcohol) $HO(1)C_6H_4(2)CH_2OH$, m.p. 86°, and glucose; dilute acids also hydrolyse it, but the saligenin is hereby resinified to saliretin. Oxidation with HNO_3 converts it to helicin (see below), the glucoside of salicylaldehyde (*Schiff*, Ann. **154**, 14), while $KMnO_4$ gives glucosalicylic acid (*Tiemann* and *Reimer*, Ber. 8, 515); hence the saligenin is attached to the glucose through the phenolic O-atom.

Populin (*benzoyl-salicin*), $C_{20}H_{22}O_8$, m.p. 180°, $[\alpha]_D$ — 53°, occurs in the bark of the aspen (*Populus tremula*) (*Piccard*, Ber. **6**, 890). Its constitution is shown by its hydrolysis with baryta to *salicin* and *benzoic acid* (*Schmidt*, Ann. **119**, 92), and by its partial synthesis from salicin and benzoyl chloride (*Schiff*, Ann. **154**, 1). Acid hydrolysis of tetramethyl-populin shows that the benzoyl group occupies the 6-position in the sugar molecule (*Richtmyer* and *Yeakel*, Am. **56**, 2495).

Helicin, *spirain*, $C_{13}H_{16}O_7$, m.p. 174–175°, $[\alpha]_D$ — 60·43°, is prepared from the roots of various species of *Spiraea*. Hydrolysis shows that it is the glucoside of *salicylaldehyde*. Its constitution is proved by its formation from salicin with nitric acid (see above) and its reconversion into this with Na amalgam (*Piria*, Ann. **96**, 378), and by its synthesis from the K salt of salicylaldehyde and acetobromoglucose (*Kopp*, Ber. **12**, 2260).

Monotropitoside, *monotropidin*, $C_{19}H_{26}O_{12} \cdot H_2O$, m.p. 92°, anhydrous m.p. 179·5°, $[\alpha]_D$ —57·65°, can be obtained from *Monotropa hypopitys*, the cherry birch, *Betula lenta*, and species of *Spiraea* (*Karrer* and *Weidmann*, Helv. **3**, 252). Its constitution as the primveroside of methyl salicylate has been proved by degradation and synthesis: careful enzymatic hydrolysis with primverosidase yields methyl salicylate and primverose (xylosido-glucose, vol. I, 724; *Helferich* and *Rauch*, Ann. **455**, 168; *Goris* and *Vischniac*, C. r. **169**, 871), while total hydrolysis with 3% H_2SO_4 gives methyl salicylate, glucose and xylose (*Bridel*, C. r. **178**, 1310; ibid. **177**, 642; J. Pharm. Chim. (7) **5**, 217; Bull. Soc. chim. biol. **5** (1923), 133; ibid. **6** (1924), 659, 679; *Bridel* and *Picard*, C. r. **180**, 1864). It has been synthesised in the following way: 2:3:4-triacetyl-methyl-salicylate-β-glucoside, obtained from methyl-salicylate-β-glucoside via the 6-trityl-ether, is treated with acetobromoxylose in benzene solution in the presence of Ag_2O; the product is hexa-acetyl-monotropitoside $C_{31}H_{38}O_{18}$, m.p. 198°, $[\alpha]_D$ — 85·8° ($CHCl_3$) which is then de-acetylated (*Robertson* and *Waters*, J. **1931**, 1881).

Violutoside, *methyl salicylate vicianoside*, m.p. 168·5°, $[\alpha]_D$ — 35·18°, obtained from *Viola cornuta*, can be hydrolysed to methyl salicylate, glucose and arabinose (*Picard*, C. r. **182**, 1167). It has been synthesised from methyl salicylate, 2:3:4-triacetyl-β-glucoside and triacetyl-arabinosyl bromide (*Robertson* and *Waters*, J. **1932**, 2770).

Avenein, $C_{14}H_{18}O_8$, m.p. 192°, $[\alpha]^{20}_D$ — 88·63°, which occurs in the roots and fruits of *Avena sativa* and the couch grass, *Triticum repens*, has been identified as glucovanillin, $O{:}CH \cdot C_6H_3 \cdot (OCH_3) \cdot (OC_6H_{11}O_5)$. It has been synthesised by the method of Michael (see p. 352, and *Fischer* and *Raske*, Ber. **42**, 1465); it is also obtained by the oxidation of coniferin (p. 357) with CrO_3 (*Tiemann*, Ber. **18**, 1595; *Tiemann* and *Kies*, ibid. 1657).

Primulaverin, $C_{20}H_{28}O_{13}$, m.p. 160°, $[\alpha]_D$ — 67·11°, and the isomeric **primverin,** m.p. 203°, $[\alpha]_D$ — 71·53°, are found in the roots of the cowslip *Primula veris*. The enzyme primverase hydrolyses them to primverose (6-β-xylosido-glucose) and methyl m-methoxy-salicylate or methyl p-methoxy-salicylate, respectively. Primverin has been synthesised in a similar way to monotropitoside (see above) (*Jones* and *Robertson*, J. **1933**, 1618).

β-Glucosido-gallic acid, $C_{13}H_{16}O_{10}$, m.p. 193° (decomp.), $[\alpha]_D$ — 21·3°, is contained in rhubarb. For its synthesis see *Fischer* and *Strauss*, Ber. **45**, 3773; *Fischer* and *Bergmann*, Ber. **51**, 1804).

Syringic acid glucoside, $C_{15}H_{20}O_{10}$, m.p. 225° (anhyd.), $[\alpha]_D$ — 18·18°, is found in the bark of *Robinia pseudacacia*; it is also obtained by a biological synthesis from syringin (see p. 357). It has been synthesised from methyl syringate (the dimethyl ether of methyl gallate) and acetobromoglucose (*Mauthner*, J. pr. **82**, 271), and from tetra-acetylglucosido-gallic acid by methylation and subsequent de-acetylation (*Fischer* and *Bergmann*, Ber. 51, 1804).

For **dryophanthin,** a glucoside of purpurogallin, see natural colouring matters, p. 425.

The **tannins,** which are sugar-esters of phenol-carboxylic acids, chiefly gallic acid, are described in their own section, p. 391.

Picein (piceoside), **salinigrin,** $C_{14}H_{18}O_7$, m.p. 194°, $[\alpha]^{25}_D$ — 88·87°, a glucoside of the silver fir, *Pinus picea*, and of the sallow, *Salix cinerea*, is decomposed by emulsin and by dilute acids into *piceol* (p-hydroxy-acetophenone) $C_8H_8O_2$, m.p. 109°, and glucose (*Rabate*, Bull. Soc. Chim. biol. **12** (1930), 965; *Jowett*, J. **1932**, 721). It has been synthesised from p-hydroxy-acetophenone and β-acetobromoglucose (*Mauthner*, J. pr. **88**, 764).

Androsin, $C_{15}H_{20}O_8 \cdot 2H_2O$, m.p. 223°, which occurs in the rhizomes of *Apocynum androsaemifolium*, is hydrolysed by emulsin to aceto-vanillone, $CH_3CO \cdot C_6H_3 \cdot (OH)(4)(OCH_3)(3)$, m.p. 115°, and glucose (*Moore*, J. **95**, 734). For its synthesis from the hydrolysis products, see *Mauthner*, J. pr. **97**, 217; **110**, 123.

Lusitanicoside, $C_{21}H_{30}O_{10}$, m.p. 188°, from Portuguese cherry laurel leaves (*Cerasus lusitanica*), is decomposed by total hydrolysis into p-allyl-phenol (chavicol) $C_6H_{10}O$, *d*-glucose and rhamnose (*Hérissey* and *Laforest*, C. r. **194**, 1095; *Hérissey*, ibid. **198**, 265).

Gein, *geoside*, $C_{21}H_{30}O_{11} \cdot H_2O$, m.p. 146°, $[\alpha]^{20}_D$ — 53·80°, is isolated from the roots of the common water-avens (*Geum urbanum*); enzymatic hydrolysis gives *eugenol*, $(HO)(CH_3O) \cdot C_6H_3 \cdot CH_2 \cdot CH{:}CH_2$, and vicianose (6-β-arabinosido-glucose; see *Helferich* and *Bredereck*, Ann. **465**, 166), which is decomposed by dilute acids into *d*-glucose and *l*-arabinose (*Hérissey* and *Cheymol*, C. r. **181**, 565; J. Pharm. Chim. (8) **3**, 156; C. r. **184**, 1307).

Coniferin, $C_{16}H_{22}O_8 \cdot 2H_2O$, $[\alpha]_D$ — 66·9°, is present in the cambial sap of the *Coniferae*, in asparagus and in the viper grass, *Scorzonera hispanica* (*v. Lippmann*, Ber. **25**, 3221; *Zemplén*, Z. physiol. Chem. **85**, 415). It loses water in the air, and, when anhydrous, melts at 185°. Moistened with phenol and conc. HCl it gives a deep-blue colour. It is hydrolysed by boiling acids or by the action of emulsin to coniferyl alcohol

$$(4)(HO)(3)(CH_3O)\cdot C_6H_3\cdot CH{:}CHCH_2OH,$$

m.p. 74°, and *d*-glucose (*Tiemann*, Ber. **11**, 672). Oxidation with CrO_3 gives glucovanillin (avenein), $C_{14}H_{18}O_8$, m.p. 192° (see p. 356), while $KMnO_4$ gives glucovanillic acid, $C_{14}H_{18}O_9$, m.p. 211–212° (*Tiemann*, Ber. **18**, 1595). After subcutaneous injection of coniferin, the K salt of vanillin-glucuronic acid is found in the urine. The oxidation of coniferin to vanillin by air in ultraviolet light is of technical interest (Germ. Pat. 224,071); for the technical preparation of vanillin from coniferin, see *Tiemann* and *Haarmann*, Ber. **7**, 613; Germ. Pat. 576 and 27,992. Coniferin has been synthesised (*Pauly* and *Feuerstein*, Ber. **60**, 1031).

Syringin, $C_{17}H_{24}O_9 \cdot H_2O$, m.p. 191–192°, $[\alpha]_D$ —17°, is contained in the bark of the lilac, *Syringa vulgaris*, the privet, *Ligustrum vulgare*, and jasmin. Emulsin yields *syringenin*, $(CH_3O)_2(HO)\cdot C_6H_2\cdot CH{:}CH\cdot CH_2OH$, and glucose. It has been proved by oxidation that the glucose residue is attached to the phenolic hydroxyl, as in coniferin. When it is administered by the mouth, syringin is degraded to syringic acid $(CH_3O)_2(HO)\cdot C_6H_2\cdot COOH$, m.p. 208°. Syringin has been synthesized as follows: syringic aldehyde is obtained by the condensation of pyrogallol-1:3-dimethyl ether with chloral, followed by oxidation; this aldehyde is condensed with acetaldehyde to yield

$$OCH\cdot CH{:}CH\cdot C_6H_2\cdot (OCH_3)_2(3{:}5)(OH)(4),$$

the K salt of which is allowed to react with acetobromoglucose; the glucosidoaldehyde is reduced to the alcohol with yeast, and the acetyl groups removed by gentle hydrolysis (*Pauly* and *Strassberger*, Ber. **62**, 2277).

Melilotoside, $C_{15}H_{18}O_8 \cdot H_2O$, m.p. 240–241°, $[\alpha]_D$ + 68·1°, obtained from the flowers of *Melilotus altissima* and *arvensis*, is hydrolysed by emulsin to *o-coumaric acid* $HO\cdot C_6H_4\cdot CH{:}CH\cdot COOH$, and glucose (*Charaux*, Bull. Soc. Chim. Biol. **7** (1925), 1056). It has been synthesised from helicin (p. 355) and malonic acid (*Shinoda* and *Imaida*, J. pharm. Soc. Japan **54** (1934), 107). This glucoside is interesting, because it forms a link with the next group of glycosides, which are derived from coumarin, the compound responsible for the scent of the woodruff (*Asperula odorata*).

The **coumarin glycosides** are derivatives of the lactone of o-hydroxycinnamic acid. The action of alkali on their aglucones therefore gives derivatives of o-coumaric acid. As they are benzo-α-pyrones, they are converted by ammonia into α-hydroxy-quinolines. The action of alcoholic potash upon their dibromides gives coumarones, which contain a five-membered heterocyclic ring.

The ring-system of coumarin can be built up from the requisite phenol and a β-aldehydo- or β-keto-acid and sulphuric acid (*v. Pechmann* and *Duisberg*, Ber. **16**, 2119; *v. Pechmann*, ibid. **17**, 929; *v. Pechmann* and *Cohen*, ibid., 2187; *Gattermann* and *Köbner*, ibid. **32**, 287; *v. Pechmann* and *Krafft*, ibid. **34**, 423; *Peters* and *Simonis*, ibid. **41**, 830). 3-Hydroxy-coumarin derivatives can be prepared from their alkali fission products (*Fantl* and *Salem*, Biochem. Z. **226**, 166), which are derivatives of o-hydroxy-benzaldehyde and glycollic acid (*Willstätter*, *Zechmeister* and *Kindler*, Ber. **57**, 1938).

Skimmin, $C_{15}H_{16}O_8 \cdot H_2O$, m.p. 210°, present in *Skimmia japonica*, is decomposed by hydrolysis into skimmetin (umbelliferone, 7-hydroxy-coumarin) $C_9H_6O_3$, m.p. 224°, and skimminose (*Eijkman*, Rec. **3**, 204). For attempts to synthesise it, see *Mauthner*, J. pr. **91**, 174.

Aesculin, $C_{15}H_{16}O_9 \cdot 2H_2O$, m.p. 160°, anhyd. 205°, $[\alpha]_D$ —146°, the glucoside of the horse chestnut (*Aesculus hippocastanum*) and of the wild jasmin (*Gelsemium sempervirens*), is hydrolysed by emulsin to *aesculetin*, 6:7-dihydroxy-coumarin $C_9H_6O_4$, m.p. 270° and *d*-glucose (*Glaser* and *Kraus*, Biochem. Z. **188**, 183; *Sigmund*, Mo. **31**, 657). The sugar residue is attached to the 6-position of the dihydroxy-coumarin, since the methylation product of aesculin yields 6-hydroxy-7-methoxy-coumarin, m.p. 185°, on hydrolysis (*Seka* and *Kallir*, Ber. **64**, 622). For its synthesis, see *Head* and *Robertson*, J. **1930**, 2434; *Macbeth*, J. **1931**, 1288. (See also p. 514).

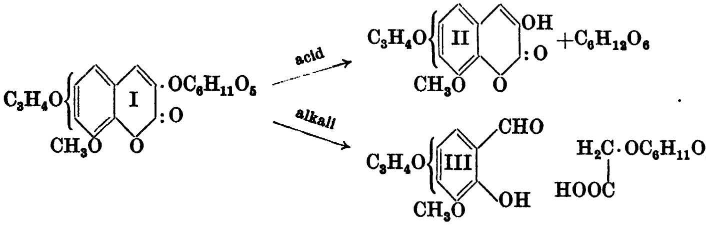
Cichoriin, $C_{15}H_{16}O_9 \cdot 2H_2O$, m.p. 215°, $[\alpha]_D$ —104·5° (in dioxan), is a structural isomer of aesculin, found in the flowers of the chicory, *Cichorium intybus*. Its constitution has been shown to be 6-hydroxy-7-glucosidoxy-coumarin by its conversion with diazomethane into the 6-methyl ether of iso-aesculin (6-methoxy-7-glucosidoxy-coumarin) $C_{16}H_{18}O_9 \cdot H_2O$, m.p. 217°. This formula is confirmed by its synthesis from aesculetin and acetobromoglucose (*Merz*, Arch. Pharm. **270** (1932), 476).

Methyl-cichoriin, *methyl-iso-aesculin*, $C_{16}H_{18}O_9$, m.p. 228°, and **scopolin,** $C_{22}H_{28}O_{14}$, m.p. 218°, which occur together in *Scopolia japonica*, give on hydrolysis scopoletin, 6-methoxy-7-hydroxy-coumarin, $C_{10}H_8O_4$, m.p. 202–203°, and one and two molecules of glucose respectively (*Seka* and *Kallir*, Ber. **64**, 909; *Head* and *Robertson*, J. **1931**, 1241; *Chou*, C. 1931 II 2891; *Merz*, N. **21**, 157).

An isomer of aesculin, **daphnin,** $C_{15}H_{16}O_9 \cdot 2H_2O$, m.p. 200° (decomp.), $[\alpha]_D$ — 52°, occurs in the bark of the spurge laurel (*Daphne alpina*). Total hydrolysis gives daphnetin, 7:8-dihydroxy-coumarin, $C_9H_6O_4$, m.p. 256° and one molecule of glucose. Its formulation as 7-glucosidoxy-8-hydroxy-coumarin is confirmed by its synthesis (*Wessely* and *Sturm*, Ber. **62**, 115; **63**, 1299; *Leone*, Gazz. **55** (1925), 673).

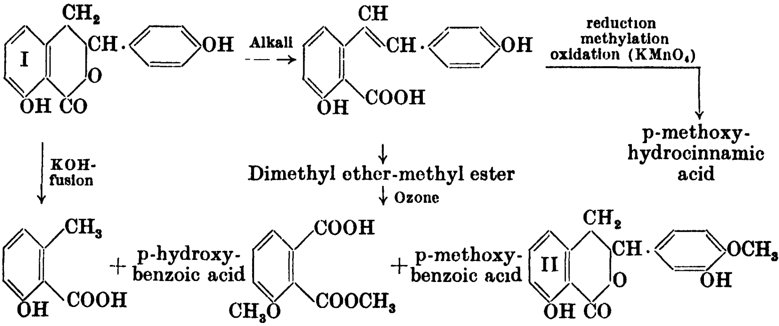
Fraxin, $C_{16}H_{18}O_{10}$, m.p. 205°, is found in the ash (*Fraxinus excelsior*) and in species of *Aesculus*. From the hydrolysis products, fraxetin, 6-methoxy-7:8-dihydroxy-coumarin $C_{10}H_8O_5$, m.p. 227–228°, and glucose have been isolated (*Wessely* and *Demmer*, Ber. **61**, 1279). The sugar component was shown to be in position 8 by a comparison with synthetic alkylation products (*idem*, Ber. **62**, 123).

Chellol-glucoside, $C_{19}H_{20}O_{10}$ (I), a bright-yellow substance m.p. 175°, found in the fruits and seed-pods of *Ammi visnaga*, a plant growing on the Nile which is known by the Arabs as "chellah". It can be hydrolysed by acids to *chellol* $C_{13}H_{10}O_5$ (II), m.p. 179°, and glucose; fission with alkali yields a phenolic aldehyde $C_{11}H_{10}O_4$ (III), m.p. 111°, and *d*-glucosido-glycollic acid $C_8H_{14}O_8$, m.p. 163–167°. These results may be expressed in the following formulae (*Fantl* and *Salem*, Biochem. Z. **226**, 166):



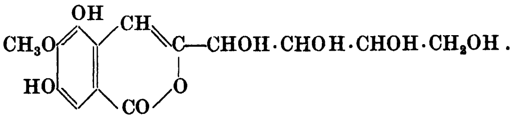
For the glycoside **nodakenin,** which contains a furo-coumarin skeleton, see p. 500.

Hydrangenol (I), $C_{15}H_{12}O_4$, m.p. 181°, a member of the isocoumarin series, occurs partly as glucoside in the flowers of the garden hydrangea (*Hydrangea opuloides*); its hydroxy methyl ether, **phyllodulcin** (II), $C_{16}H_{14}O_5$, m.p. 105–110°, is present in the leaves of the same plant. The constitution of the former has been proved by the following degradation (*Asahina* and *Asano*, Ber. **62**, 171; **63**, 429):



The formula of phyllodulcin (II) is based on a corresponding series of reactions. Both compounds may be built up by a method based upon Gabriel's benzalphthalide synthesis (*idem*, Ber. **63**, 2059; **64**, 1252).

The bitter substance **bergenin** $C_{14}H_{16}O_9 \cdot H_2O$, m.p. 141°, anhyd. 234°, $[\alpha]_D$ — 51°, is isolated from the rhizome of the saxifrage *Saxifraga crassifolia* (*Tchitchibabin*, Ann. **469**, 93); this also is an iso-coumarin derivative. Of the 9 oxygen atoms present, 6 are shown by Zerevitinov's method to be present as hydroxyl, and 2 of these are phenolic (di-Na salt, dimethyl ether); further, the presence of a lactone group is shown by titration, and there is also one methoxyl group. Oxidation of dimethyl-bergenin with permanganate throws considerable light upon its structure: in addition to trimethoxy-o-phthalic acid, 5:6:7-trimethoxy-isocoumarin-3-carboxylic acid and 5:6:7-trimethoxy-isocoumarin are obtained. The proof of the ring-system is based further upon the conversion of both of the latter degradation products and of bergenin itself into the corresponding isoquinoline derivatives (*Tchitchibabin*, Russ. Pat. 15,110; C. 1932 I 3322). Fusion of bergenin with potash yielded 4-methoxy-3:5-dihydroxybenzoic acid; this gave the position of the methoxyl group in the isocoumarin ring. The aliphatic residue of the molecule, $C_4H_9O_4$, with 4 active H-atoms and 4 hydroxyl groups capable of acetylation, could only be an erythritol side-chain. These experimental results are expressed in the following formula:



Phlorrhizin, *asebotoside*, $C_{21}H_{24}O_{10} \cdot 2H_2O$, m.p. 109°, anhyd. 171°, $[\alpha]_D$ — 50·02°, is closely related to the flavanone glycosides treated below. It is found in the bark of the roots of various fruit trees, hence its name, from *φλοιός* bark, and *ῥίζα* root (*Fischer*, Ber. **21**, 988); it is also present in *Rosaceae* and *Ericaceae* (*Bridel* and *Kraner*, C. r. **193**, 748) and in the leaves of *Kalmia latifolia* (*idem*, Bull. Soc. Chim. Biol. **15** (1933), 531). It produces strong glucosuria (Klin. Woch. **16**, 431). The glucoside is hydrolysed by emulsin or by hot dilute mineral acids into glucose and *phloretin*

$$(4')(HO) \cdot C_6H_4 \cdot CH_2 \cdot CH_2 \cdot CO \cdot C_6H_2(OH)_3(2:4:6),$$

m.p. 248° (*Bridel*, J. Pharm. Chim. (8) **12**, 385; Bull. Soc. Chim. Biol. **12** (1930), 921; *Moelwyn-Hughes*, Trans. Faraday Soc. **24**, 309); the latter is decomposed by concentrated alkali into phloretic acid, p-hydroxy-hydrocinnamic acid

$C_9H_{10}O_3$, m.p. 128°, and phloroglucinol $C_6H_6O_3$ (*Strecker*, Ann. **74**, 184; *Schiff*, Ann. **156**, 1). Phlorrhizin itself undergoes fission with alkali to give phloretic acid and phloroglucinol-glucoside, $C_{12}H_{16}O_8$, m.p. 239° (dec.), $[\alpha]_D$ — 74·79° (synthesis: *Fischer* and *Strauss*, Ber. **45**, 2467; *Cremer* and *Seuffert*, ibid. 2565). For the synthesis of phloretin from phloroglucinol and acetyl-phloretic nitrile, see *Fischer* and *Nouri*, Ber. **50**, 611; *Wessely* and *Sturm*, Mo. **53/54**, 554. Since the phloretin derivative

$$(CH_3O)_2(HO)\cdot C_6H_2\cdot CO\cdot CH_2\cdot CH_2\cdot C_6H_4(OCH_3),$$

m.p. 110°, obtained by the removal of glucose from the trimethyl ether of phlorrhizin (m.p. 76°), is identical with synthetic unsymmetrical trimethyl-phloretin, and further since this can be converted by Na acetate and acetic anhydride into the corresponding methyl-benzopyrone compound $C_{20}H_{20}O_5$, m.p. 166°, the sugar group in phlorrhizin must occupy one of the ortho-hydroxyl groups (*Johnson* and *Robertson*, J. **1930**, 21). Its pyranose structure follows from the formation of 2:3:4:6-tetramethylglucose m.p. 94°, together with trimethyl-phloretin, by the hydrolysis of phlorrhizin-heptamethyl ether (*Müller* and *Robertson*, J. **1933**, 1170).

The leaves of *Smilax glycyphylla* contain **glycyphyllin,** $C_{21}H_{24}O_9\cdot 3H_2O$, m.p. 175–180°, the rhamnoside of *phloretin* (*Wright*, *Rennie*, Chem. News **54**, 258; J. **39**, 237; **49**, 857).

The constitution of the **flavanone glycosides** has been fully confirmed by the fact that on reduction they are converted into the corresponding anthocyanidins (*Asahina* and *Inubuse*, Ber. **61**, 1646; *Asahina*, *Nakagome* and *Inubuse*, Ber. **62**, 3016); the spectroscopic results also point to a benzopyrane ring-system (*Shibata* and *Nagai*, Acta Phytochim. **2** (1924), 25). Energetic methylation or acetylation opens the ring to give chalkones (*Asahina*, *Shinoda* and *Inubuse*, J. Pharm. Soc. Japan **1927**, 133; *Shinoda* and *Inubuse*, ibid. **48**, 29; *Asahina* and *Inubuse*, Ber. **61**, 1514); see natural colouring matters, p. 436.

Liquiritin, $C_{21}H_{22}O_9$, m.p. 212°, the glycoside of *Glycyrrhiza glabra* (*Radix Liquiritiae*), has as its aglycone *liquiritigenin*, $C_{15}H_{12}O_4$, m.p. 207°, a 7:4′-dihydroxy-flavanone (*diacetate* m.p. 186°, *oxime* m.p. 178°). The structure of this follows from its fission with 50% KOH to resacetophenone, m.p. 144°, (*oxime* m.p. 204°), and p-hydroxybenzoic acid, m.p. 210°; the position of the glucose residue is shown to be on the 4′-hydroxyl by the action of alkali on liquiritin methyl ether, which gives paeonol, m.p. 52° (*oxime* m.p. 131·5°), and p-hydroxybenzoic acid (*Shinoda* and *Ueeda*, Ber. **67**, 434).

Citronin, $C_{22}H_{24}O_{10}$, from species of *Citrus*, is the glucoside of *citronetin*, $C_{16}H_{14}O_5$, m.p. 225°, which is identified as 5:7-dihydroxy-2′-methoxy-flavanone by its synthesis from phloroglucinol and o-methoxy-cinnamaldehyde (*Shinoda* and *Sato*, J. Pharm. Soc. Japan **51** (1931), 78).

Naringin, $C_{27}H_{32}O_{14}$, a yellowish substance, m.p. 171° (anhyd.), $[\alpha]_D$ —84·07°, is found particularly in the flowers and also in other parts of the tree *Citrus decumana*, which grows in Java (*Will*, Ber. **18**, 1316). The name of the glucoside is derived from "naringi", the Sanskrit word for orange. Hydrolysis with dilute acids yields (*Asahina* and *Inubuse*, Ber. **61**, 1514; *Zeller*, Ind. Eng. Chem. **10**, 364) glucose, rhamnose and naringenin $C_{15}H_{12}O_5$, m.p. 248° (5:7:4′-trihydroxy-flavanone; synthesis: *K. Rosenmund* and *M. Rosenmund*, Ber. **61**, 2608). The latter is decomposed by KOH into phloroglucinol and p-hydroxy-cinnamic acid (*Will*, Ber. **18**, 1316; **20**, 297); it is hydrogenated catalytically to phloretin (p. 359), and is reduced by Na amalgam to the corresponding benzopyrylium compound, apigenidin (apigenidin chloride, m.p. > 300°, deep-violet) (*Asahina* and *Inubuse*, Ber. **61**, 1646; **62**, 3016).

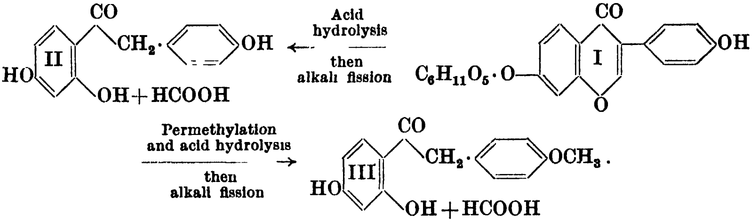
Sakuranin, $C_{22}H_{24}O_{10}$, white needles, m.p. 212°, $[\alpha]_D$ —106°, is the glucoside from the Japanese cherry tree *Prunus pseudocerasus*. Its constitution is based upon its degradation to sakuranetin $C_{16}H_{14}O_5$, m.p. 150° (7-monomethyl ether of naringenin), and upon its synthesis (*Asahina, Shinoda* and *Inubuse*, J. Pharm. Soc. Japan **1927**, 133; *Shinoda* and *Sato*, ibid. **48** (1928), 109, 117).

Hesperidin, *diosmin, barosmin,* $C_{28}H_{34}O_{15}$, colourless, m.p. 251°, occurs in unripe oranges and lemons (*Tiemann* and *Will*, Ber. **14**, 948). Hydrolysis gives glucose, rhamnose, and *hesperetin* $C_{16}H_{14}O_6$, m.p. 228° (5:7:3′-trihydroxy-flavanone); alkali fission of the latter gives phloroglucinol and hesperetic acid, m.p. 238° (isoferulic acid, p-methoxy-m-hydroxy-cinnamic acid) (see *Asahina, Shinoda* and *Inubuse*, J. Pharm. Soc. Japan **48** (1928), 29; *Shinoda* and *Sato*, ibid. **49** (1929), 5; *Asahina* and *Inubuse*, ibid., 11). The synthesis of hesperetin is described by *Shinoda* and *Kawagoye*, ibid. **48** (1928), 119).

The **flavones, flavonols** and **anthocyanidins**, and probably brasilin and haematoxylin also, occur in plants almost entirely as glycosides; these are described under the natural colouring matters, p. 440.

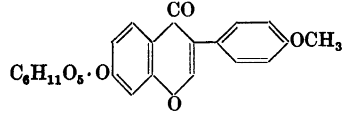
The **isoflavone glycosides** differ essentially from those of the isomeric flavones in giving derivatives of phenyl-benzyl ketone and formic acid when they are decomposed with alkali; by treatment of the ketone with formic ester or with acetic anhydride and sodium acetate the ring can be closed once more to the corresponding isoflavone.

Daidzin (I), $C_{21}H_{20}O_9$, almost colourless needles of m.p. 235°, $[\alpha]_D$ —36·7°, from *Soja hispida*, is hydrolysed to glucose and daidzein (7:4′-dihydroxy-isoflavone) $C_{15}H_{10}O_4$, m.p. 323° (dimethyl ether m.p. 164°; diacetate m.p. 181°); alkali fission of the latter gives the ketone (II), $C_{14}H_{12}O_4$, m.p. 192°, and formic acid, from which components it can be once more built up (*Wessely, Kornfeld* and *Lechner*, Ber. **66**, 685; *Mahal* and *Rai*, and *Venkataraman*, J. **1934**, 1769). After complete methylation, alkali fission gives the ketone (III), $(HO)_2C_6H_3\cdot CO\cdot CH_2\cdot C_6H_4(OCH_3)$, m.p. 158°, and hence the glucose molecule must be attached to the 7-hydroxyl of the benzopyrone ring (*Walz*, Ann. **489**, 129). The following formulae show these degradations:



A partial synthesis has been described from 2-methyl-7:4′-dimethoxy-isoflavone, via the 2-benzylidene-compound and the 2-carboxylic acid (*Baker, Robinson* and *Simpson*, J. **1933**, 274).

Ononin, $C_{22}H_{22}O_9$, m.p. 210°, the 4′-methyl ether of daidzin, occurs in the roots of the restharrow, *Ononis spinosa* (*Hemmelmayr*, Mo. **23**, 144; **25**, 555). Its various fission products are shown in the following scheme (*Wessely* and *Lechner*, Mo. **57**, 395):



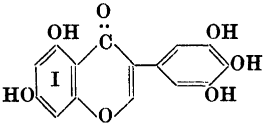
Acids
— →Glucose + Formononetin m.p. 265°
(7-hydroxy-4′-methoxy-isoflavone)
Baryta
— →HCOOH + Onospin, m.p. 172°
(Glucosido-ononetin)

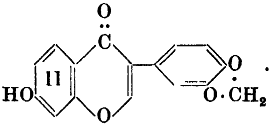
Baryta
- - —→Ononetin, m.p. 158° + HCOOH
$(HO)_2C_6H_3\cdot CO\cdot CH_2\cdot C_6H_4(OCH_3)$
Acids
———→Ononetin, m.p. 158° + Glucose.

The constitution of ononetin has been established by synthesis; when condensed with formic ester it is reconverted to formononetin (*Wessely, Kornfeld* and *Lechner*, Ber. **66**, 685; *Wessely, Lechner* and *Dinjaski*, Mo. **63**, 201).

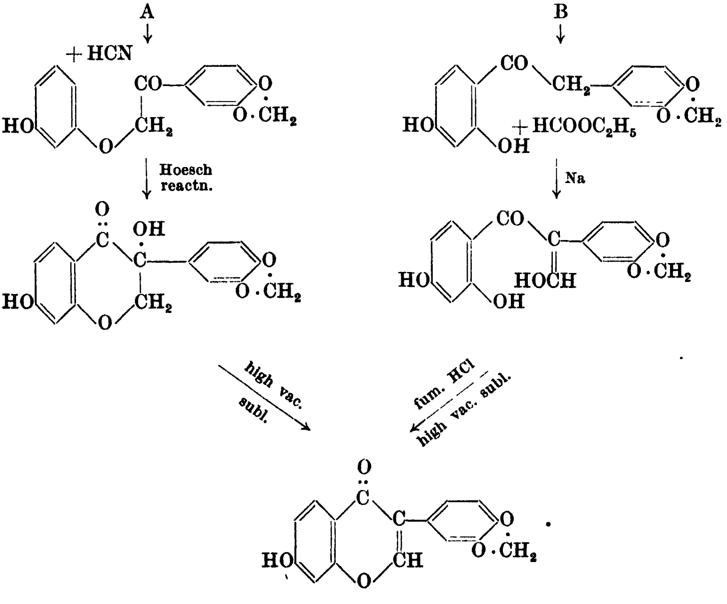
Genistin, $C_{21}H_{20}O_{10}$, yellow plates m.p. 254–256°, $[\alpha]_D$ —27·7°, is found with daidzin in *Soja hispida*. Hydrolysis with acids yields genistein $C_{15}H_{10}O_5$, m.p. 297–298° (5:7:4′-trihydroxy-isoflavone) and glucose; alkali fission of the aglucone gives HCOOH and the ketone $(HO)_3C_6H_2 \cdot CO \cdot CH_2 \cdot C_6H_4(OH)$, m.p. 253–257°, the constitution of which is shown by the products of its fusion with potash, viz. phloroglucinol and p-hydroxy-phenylacetic acid. As the completely methylated genistin is hydrolysed by acids to 7-hydroxy-5:4′-dimethoxy-isoflavone, the glucoside itself must be 7-glucosidoxy-5:4′-dihydroxy-isoflavone.

Baptisin, $C_{27}H_{32}O_{15}$, m.p. 240°, $[\alpha]_D$ —61°, and **pseudo-baptisin,** $C_{28}H_{28}O_{14} \cdot 3H_2O$, m.p. 247–248°, $[\alpha]_D$ —101·1°, are found in the roots of *Baptisia tinctoria*. Acid hydrolysis yields respectively baptigenin, $C_{15}H_{10}O_7$ (I), m.p. > 250°, and 2 mol. rhamnose, and pseudo-baptigenin $C_{16}H_{10}O_5$ (II), m.p. 298°, *d*-glucose and rhamnose. The constitutions of the two aglycones (I) and (II) have been established by the usual method of alkali degradation (*Gorter*, Arch. Pharm. **235** (1897), 303; **244** (1906), 401; *Spath* and *Schmidt*, Mo. **53/54**, 454):



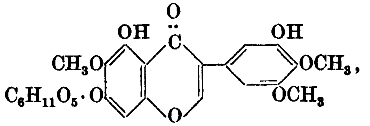


The position of the sugar residues is still undetermined. ψ-Baptigenin has been synthesised in two ways, from resorcinol and 3:4-methylene-dihydroxy-ω-bromacetophenone (A), and from resorcinol and 3:4-methylene-dihydroxybenzyl cyanide (B), via the following intermediates (*Späth* and *Lederer*, Ber. **63**, 743):



Tectoridin, $C_{22}H_{22}O_{11}$, m.p. 258°, a glucoside from the rhizomes of *Iris tectorum* (Japan), gives with hot dilute sulphuric acid glucose and tectorigenin $C_{16}H_{12}O_6$, m.p. 227°; alkali fission of the latter gives p-hydroxy-phenylacetic acid and the ketone $(HO)_3\cdot(CH_3O)C_6H\cdot CO\cdot CH_2C_6H_4(OH)$, which is further converted into iretol, m.p. 186° (1:3:5-trihydroxy-4-methoxy-benzene); hence the aglucone is 5:7:4′-trihydroxy-6-methoxy-isoflavone.

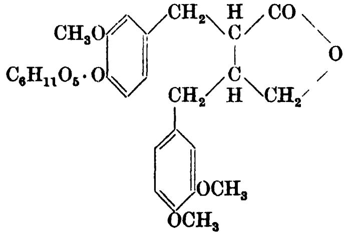
The root-nodules of the Florentine orris (*Iris florentina*) contain the glucoside **iridin** $C_{24}H_{26}O_{13}.H_2O$, white needles m.p. 208°, anhyd. m.p. 217°. Hydrolysis with H_2SO_4 yields glucose and irigenin $C_{18}H_{16}O_8$, m.p. 186°, which is degraded by conc. KOH to iridic acid $C_{10}H_{12}O_5$, m.p. 118° (3-hydroxy-4:5-dimethoxy-phenylacetic acid), iretol, $C_7H_8O_4$, m.p. 186° (see above) and formic acid. Iridic acid can be decarboxylated to iridol $C_9H_{12}O_3$, m.p. 57° (3-hydroxy-4:5-dimethoxy-1-methylbenzene) (*de Laire* and *Tiemann*, Ber. **26**, 2010; *Nickel*, Chem. Ztg. **18**, 531). The final formula for the glucoside



has been proved by synthesis (*Baker*, J. **1928**, 1022; *Baker* and *Robinson*, J. **1929**, 152; *Shinoda* and *Sato*, J. Pharm. Soc. Japan **52** (1932), 139).

The **xanthone glycosides,** e.g. euxanthin, are described under natural colouring matters (see p. 452).

Among the phenol resins which occur in nature (see Tannins, p. 397) there is one substance which is a glycoside. This is **arctiin,** $C_{27}H_{34}O_{11}\cdot H_2O$, which is prepared from the seeds of the burdock *Arctium Lappa* (*Shinoda* and *Kawagoye*, J. Pharm. Soc. Japan **49** (1929), 94). The aglycone arctigenin $C_{21}H_{24}O_6$, α-form m.p. 102°, $[\alpha]_D$ —28·69° (methyl ether m.p. 131–132°), is converted on heating for some time into the β-form, m.p. 92°, $[\alpha]_D$ +83·69°; it is a lactone, and the lactone ring can be opened to arctigenic acid, α-form m.p. 131° (methyl ether m.p. 97–98°), β-form m.p. 82°. Its ethyl ether is oxidised by $KMnO_4$ to degradation products which are typical of this class of compound, veratric acid and ethyl-vanillic acid (*Shinoda*, J. Pharm. Soc. Japan **49** (1929), 183; *Omaki*, ibid. **55** (1935), 159). It therefore has the following constitution (see *Haworth* and *Kelly*, J. **1936**, 998):



The **anthranol glycosides** are hydrolysed to products which show a yellow colour and a green fluorescence on the addition of borax (*Schouteten's* reaction for anthranols or anthrones). The aglucones are converted by oxidation in air into the corresponding anthraquinones. For their physiological action, see p. 496.

Aloin, aloe-emodin-anthranol-*d*-arabinoside, $C_{20}H_{20}O_8\cdot{}^1/_2H_2O$, which occurs in most kinds of *Aloe*, gives, when boiled for half an hour with borax solution and then acidified, *aloe-emodin-anthranol* (1:8-dihydroxy-3-hydroxymethyl-anthran-9-ol) $C_{15}H_{12}O_4$, m.p. 195°; this can be oxidised to aloe-emodin (cf. p. 429), and reduced to chrysophanol-anthranol (*Rosenthaler*, C. 1934 I 3347). The fact that the glucoside does not give at first the anthranol reaction shows that the sugar component occupies the meso position (*Hauser*, C. 1931 II 1709; *Rosenthaler*, Arch. Pharm. **270** (1932), 214; C. 1932 I 3320).

Barbaloin, $C_{20}H_{18}O_9$, which accompanies aloin, is probably an arabinoside of aloe-emodin (*Léger*, Bull. **3** (1936), 435).

Peristaltin ("Ciba") from *Cortex Rhamni purshianae*, contains the rhamnosides of the anthranols of chrysophanic acid, frangula-emodin-monomethyl ether and cascarol.

The **anthraquinone glycosides,** which are very deeply coloured, are also described under the natural colouring matters (p. 427).

(d) GLYCOSIDES WITH COMPLEX RING SYSTEMS

This group includes the **sterolins,** the glycosidic compounds of the sterols.

Sitosterol-d-glucoside, *ipuranol*, $C_{35}H_{60}O_6$, m.p. 300–305°, is widely distributed in nature; it has been obtained from *Trifolium pratense, Ipomea purpurea, Cluytia similis*, from the olive tree, from the leaves of *Ginkgo biloba* (*Furukawa*, C. 1932 II 3901), and many others (*Power* and *Salway*, J. **97**, 231; *Haar*, Rec. **48** (1929), 726; *Katti* and *Puntambekar*, J. Indian Chem. Soc. **7**, 221; *Katti* and *Shintre*, Arch. Pharm. **268** (1930), 314; *Power* and *Moore*, J. **99**, 937; *Tutin* and *Clewer*, J. **101**, 2221; etc.). For synthetic work, see *Salway*, J. **103**, 1022.

Phytosterolin, *gloriosol*, $C_{35}H_{60}O_6$, m.p. 285–290° (*tetracetate* m.p. 167°), $[\alpha]_D$ —22·4° ($CHCl_3$), is found in wheat germ (*Nakamura* and *Ichiba*, C. 1931 I 3015) and in the tubers of the lily *Gloriosa superba* (*Clewer, Green* and *Tutin*, J. **107**, 842). Hydrolysis with 15% HCl in amyl alcohol gives glucose and phytosterol, m.p. 137°, $[\alpha]_D$ —42° (acetate m.p. 127°), a mixture of sitosterol and stigmasterol (*Schmid* and *Bilowitzki*, Mo. **49**, 98).

Spinasterol-glucoside, $C_{34}H_{56}O_6$, m.p. 280°, $[\alpha]_D$ —33° (in pyridine); see *Heyl* and *Larsen*, Am. **56**, 942.

Under the name *saponins* there is grouped a large number of glycosides which are widely distributed in nature; these compounds give frothy, soap-like solutions (their name is derived from the Latin *sapo*, soap), and for the most part have an intensely bitter taste and a strong haemolytic action, which is increased by the addition of cholesterol (*Windaus*, Ber. **42**, 238). Hydrolysis with acids yields various sugars (galactose, *d*-glucose, *l*-arabinose) and the sapogenins (*Hoffmann*, Ber. **36**, 2722). Because of their toxic properties they are dealt with under the non-nitrogenous poisons (p. 512).

For numerous glycosides with an aglycone of undetermined structure, see *van Rijn*, Die Glykoside (*Borntrager*, Berlin 1931), and *Bergmann* and *Gierth*, Klein's Handbuch der Pflanzenanalyse, Vol. III, p. 1173 et seq. (*Springer*, Vienna 1932).

(e) NITROGENOUS GLYCOSIDES

The **prussic acid glycosides** are characterised by the formation of HCN as well as of the aglycone and sugar when they are hydrolysed by emulsin. With alkali they are hydrolysed as nitriles, and subsequent treatment with dilute acid yields the corresponding α-hydroxy-acid and the sugar component. Conc. HCl hydrolyses them direct to hydroxy-acid, sugar and ammonia.

The active principle of the nitrile-glycosides is the HCN set free from them by hydrolysis. This acts as a stimulant in small doses ("kirschwasser"), but in greater concentrations it has a paralysing effect upon the respiratory centres. It is also a strong poison for the ferments of the living cell, with the exception of the plant protease papain from the melon tree (*Carica papaya*), which is activated by HCN.

Linamarin (phaseolunatin), $C_{10}H_{17}O_6N \cdot H_2O$, m.p. 142°, $[\alpha]_D$ — 29·1°, is found in young flax (*Linum usitatissimum*) and in *Phaseolus lunatus*. Hydrolysis with emulsin yields *acetone*, glucose and HCN (*Dunstan* and *Henry*, Proc. Roy. Soc. **72**, 285); aqueous alkali forms ammonia and phaseolunatic acid, $C_{10}H_{18}O_8$, which is hydrolysed by dilute sulphuric acid to α-hydroxyisobutyric acid and glucose (*Power* and *Lees*, J. **87**, 349). It has been synthesised by a method similar to that for mandelic nitrile glucoside (see p. 366, and *Fischer* and *Anger*, Ber. **52**, 854; C. 1918 I 1163).

Hiptagin, $C_{10}H_{14}O_9N_2 \cdot {}^1/_2H_2O$, m.p. 110°, $[\alpha]_D$ + 3·5°, which occurs in the root-bark of *Hiptaga madablota*, is hydrolysed by acids to glucose and, instead of the expected hiptagenin, tartronic acid, ammonia and HCN; dry distillation gives CO_2, NH_3 and hiptagenic acid $C_3H_5O_4N$, m.p. 68° (*Gorter*, C. 1921 I 91).

The oily seeds of *Gynocardia odorata* yield the glucoside **gynocardin** $C_{13}H_{19}O_9N$, m.p. 163°, $[\alpha]_D$ + 72·5°. An enzyme from *Gynocardia* hydrolyses it to the *diketone* $C_6H_8O_4$ (?), glucose and HCN; baryta gives an acid $C_7H_{10}O_6$(?) (*de Jong*, Rec. **30** (1911), 220; *Brill*, Philippine J. Sci. **12** (1917) A, 37; *Floriani*, C. 1929 I 761).

Amygdalin, *l*-mandelic nitrile gentiobioside, $C_{20}H_{27}O_{11}N$, or $C_6H_5CH(CN)OC_{12}H_{21}O_{10} \cdot 3H_2O$, m.p. 215° (anhyd.), $[\alpha]_D$ — 40·5°, white shining plates, is found in bitter almonds, in the fruit-kernels of many species of *Prunus*, such as in cherries, peaches, apricots, etc., and in the leaves of the cherry laurel.

History:—Amygdalin was discovered in 1830 by *Robiquet* and *Boutron-Chalard* (A. ch. phys. [2] **44**, 352); its nature and constitution were explained by *Liebig* and *Wohler* (Ann. **22**, 1); it was synthesised by *Haworth* (J. **125**, 1337) by the process suggested by *E. Fischer* (see p. 366, and *Fischer* and *Bergmann*, Ber. **50**, 1047).

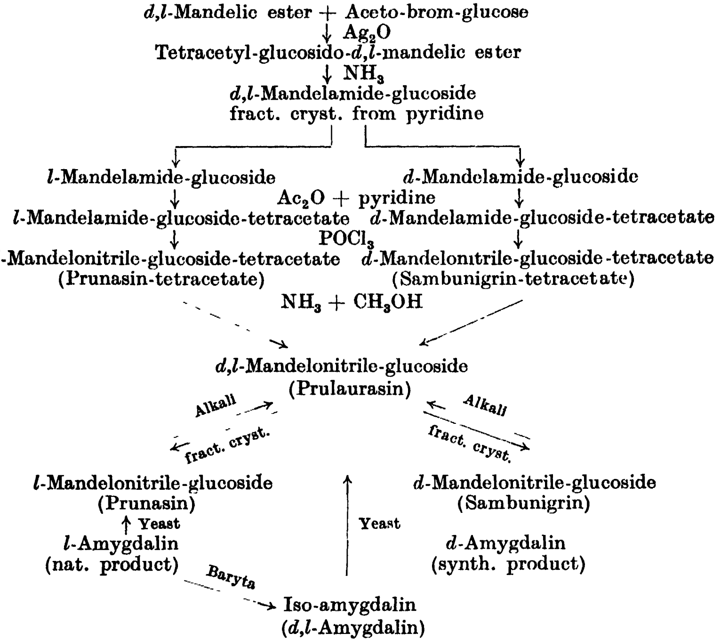
When it is boiled with dilute acids, or left to stand with water and emulsin, an enzyme contained in bitter almonds, amygdalin decomposes into two molecules of glucose, *benzaldehyde* and HCN (*Hesse*, Ann. **176**, 114). The enzyme from the intestine of the snail yields *benzaldehyde-cyanhydrin* and the disaccharide gentiobiose (6-β-glucosido-glucose, vol. I, p. 728) (*Haworth* and *Wylam*, J. **123**, 3120; *Kuhn*, Ber. **56**, 857).

With yeast, amygdalin splits off only one molecule of glucose, and gives **prunasin,** *l*-mandelic nitrile glucoside $C_6H_5CH(CN)OC_6H_{11}O_5$, m.p. 148°, $[\alpha]_D$ — 27°, which also occurs in various species of *Prunus* (*Hérissey*, J. Pharm. Chim. (6) **26**, 194), and in *Photina serrulata* (*Power* and *Moore*, J. **97**, 1099) and *Eremophila maculata* (*Finnemore* and *Cox*, Proc. Roy. Soc. N.S.W. **63** (1930), 172). Emulsin decomposes it into benzaldehyde, HCN and glucose with the intermediate formation of *d*-mandelic nitrile; conc. HCl gives glucose, ammonia and *l*-mandelic acid (*Fischer*, Ber. 28, 1508).

If amygdalin is boiled with alkalis, ammonia is evolved with the formation of *amygdalic acid* $C_6H_5CH(COOH)OC_{12}H_{21}O_{10}$; this compound has been isolated in combination with amygdalin as laurocerasin (amorphous amygdalin) from the leaves of *Prunus Laurocerasus* (*Schiff*, Ann. **154**, 339).

Shaking with dilute baryta converts amygdalin into the isomeric *iso-amygdalin*, rac. amygdalin, $[\alpha]_D$ — 47·6° (*Dakin*, J. **85**, 1512; *Zemplén*, Z. physiol. Chem. **85**, 415); this is hydrolysed by yeast into glucose and **prulaurasin,** *dl*-mandelic nitrile glucoside, m.p. 123–125°, $[\alpha]_D$ — 53·06° (*Hérissey*, J. Pharm. Chim. (6) **26**, 198). The latter compound has been isolated from the leaves of *Prunus Laurocerasus* (*Caldwell* and *Courtauld*, J. **91**, 671), and gives on hydrolysis with conc. HCl glucose, *d,l*-mandelic acid and ammonia. It is isomeric with **sambunigrin,** *d*-mandelic nitrile glucoside, m.p. 151°, $[\alpha]_D - 76 \cdot 3°$, which is obtained from the leaves of *Sambucus niger* (*Bourquelot* and *Danjou,* C. r. **141**, 598) and of *Acacia glaucescens* (*Finnemore* and *Cox,* Proc. Roy. Soc. **62** (1929), 369), and gives on hydrolysis with conc. HCl glucose, *d*-mandelic acid and ammonia. On treatment with baryta water it is racemised, like *l*-mandelic nitrile glucoside, into prulaurasin (*Caldwell* and *Courtauld,* J. **91**, 671).

The *synthesis* of prulaurasin, prunasin and sambunigrin (see *Fischer* and *Bergmann,* Ber. **50**, 1047) has been carried out in the following way; the scheme also shows the relationships of the glucosides to each other:


d,l-Mandelic ester + Aceto-brom-glucose
Ag_2O
Tetracetyl-glucosido-*d,l*-mandelic ester
NH_3
d,l-Mandelamide-glucoside
fract. cryst. from pyridine
l-Mandelamide-glucoside
d-Mandelamide-glucoside
Ac_2O + pyridine
l-Mandelamide-glucoside-tetracetate
d-Mandelamide-glucoside-tetracetate
$POCl_3$
l-Mandelonitrile-glucoside-tetracetate
(Prunasin-tetracetate)
d-Mandelonitrile-glucoside-tetracetate
(Sambunigrin-tetracetate)
$NH_3 + CH_3OH$
d,l-Mandelonitrile-glucoside
(Prulaurasin)
Alkali
fract. cryst.
Alkali
fract. cryst.
l-Mandelonitrile-glucoside
(Prunasin)
Yeast
l-Amygdalin
(nat. product)
Yeast
d-Mandelonitrile-glucoside
(Sambunigrin)
d-Amygdalin
(synth. product)
Baryta
Iso-amygdalin
(*d,l*-Amygdalin)

Amygdalin has been synthesised in an analogous way, starting from *d,l*-mandelic ester and heptacetyl-β-bromogentiobiose (*Campbell* and *Haworth,* J. **125**, 1337; *Kuhn* and *Sobotka,* Ber. **57**, 1767).

Vicianin, $C_{19}H_{25}O_{10}N$, m.p. 147–148°, $[\alpha]_D - 20 \cdot 7°$, obtained from the seeds of the wild vetch (*Vicia angustifolia*), is hydrolysed by the enzyme vicianase to benzaldehyde, HCN and vicianose (6-*l*-arabinosido-*d*-glucose, see *Helferich* and *Bredereck,* Ann. **465**, 166); the latter is hydrolysed by emulsin to *d*-glucose and *l*-arabinose (*Bertrand,* C. r. **143**, 832).

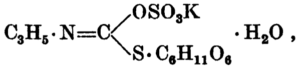
Dhurrin, $C_{14}H_{17}O_7N$, occurring in the leaves of the great millet (*Sorghum vulgare*), is a p-hydroxy-mandelonitrile-glucoside. It is hydrolysed by emulsin to p-hydroxy-benzaldehyde, HCN and glucose, with alkali to NH_3 and dhurric acid, $C_{14}H_{18}O_9$, and with HCl to p-hydroxy-mandelic acid and glucose (*Dunstan* and *Henry,* Chem. News **85**, 301).

The glucoside from *Lotus arabicus,* **lotusin,** $C_{28}H_{31}O_{16}N$, a pale-yellow substance of m.p. > 300°, is the cyanhydrin-glucoside of lotoflavin (5:7:2′:4′-tetrahydroxy-flavone, see p. 444), $C_{15}H_{10}O_6$, a yellow compound, m.p. > 200° (*Dunstan* and *Henry,* Chem. News **84**, 26).

The **mustard oil glycosides,** $R\cdot N{=}\overset{\diagup OSO_3K}{C}{—}S\cdot C_6H_{11}O_5$, are hydrolysed by myrosinase (sinigrase), an enzyme complex of thioglucosidase and a sulphatase (*Neuberg* and *v. Schoenebeck*, N. **21**, 404), into a *mustard oil*, $KHSO_4$ and glucose. Silver nitrate decomposes them into the sugar and the Ag salt of the aglucone (*Schneider*, *Fischer* and *Specht*, Ber. **63**, 2787), which is easily decomposed by alkali salts into a mustard oil and an alkali sulphate. The glucose is combined with the aglucone through the sulphur atom, as is proved by the isolation of thioglucose after hydrolysis with potassium methoxide (*Schneider* and *Clibben*, Ber. **47**, 2218; *Schneider* and *Wrede*, ibid. 2225).

Mustard oils cause local inflammations of the skin, and after resorption cause irritation of the respiratory passages. Internally they promote secretion and resorption, hence their use as a spice; larger doses produce excitation and finally paralysis of the central nervous system.

Sinigrin, "*potassium myronate*", $C_{10}H_{18}O_{10}S_2NK$,

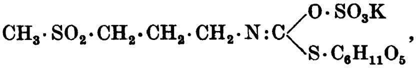


$$C_3H_5\cdot N{=}C\begin{array}{l}\diagup OSO_3K\\ \diagdown S\cdot C_6H_{11}O_6\end{array}\cdot H_2O\,,$$

m.p. 127°, anhyd. 132°, $[\alpha]_D$ — 17·6°, is found in the seeds of the black mustard (*Sinapis nigra*), and also in the horse-radish (*Cochlearia armorica*) (*Heiduschka* and *Zwergal*, J. pr. **182**, 201). Hot baryta or the ferment myrosinase contained in the mustard seeds hydrolyse it to *d*-glucose, allyl isothiocyanate $C_3H_5\cdot N{:}C{:}S$, b.p. 151°, and potassium hydrogen sulphate (*Gadamer*, Ber. **30**, 2322; *Schneider* and *Wrede*, Ber. **47**, 2225; *Wrede, Banik* and *Brauss*, Z. physiol. Chem. **126**, 210).

The seeds of the rape, *Brassica napus*, contain **glyconapin,** the glucoside of crotonyl isothiocyanate $C_4H_7\cdot N{:}C{:}S$, b.p. 179°.

Glucocheirolin, $C_{11}H_{20}N_{11}S_3NK\cdot H_2O$ or



$$CH_3\cdot SO_2\cdot CH_2\cdot CH_2\cdot CH_2\cdot N{:}C\begin{array}{l}\diagup O\cdot SO_3K\\ \diagdown S\cdot C_6H_{11}O_5\end{array},$$

m.p. 160°, $[\alpha]_D^{20}$ — 21·5°, obtained from the seeds of the yellow wallflower, *Cheiranthus Cheiri*, and from other *Cruciferae*, is decomposed by myrosinase into cheirolin $CH_3\cdot SO_2\cdot CH_2\cdot CH_2\cdot CH_2\cdot N{:}C{:}S$, m.p. 48°, glucose and $KHSO_4$ (*Schneider* and *Lohmann*, Ber. **45**, 2954; *Schneider* and *Schutz*, Ber. **46**, 2634). With silver nitrate, the glucoside undergoes fission to glucose and the silver salt of cheirolin-sulphate, which decomposes readily into sulphate and cheirolin (*Schneider*, Ann. **386**, 346).

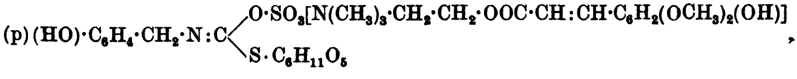
A homologue of cheirolin, **erysolin,** $C_6H_{11}O_2S_2N$,

$$CH_3\cdot SO_2\cdot CH_2\cdot CH_2\cdot CH_2\cdot CH_2\cdot N{:}C{:}S,$$

m.p. 60°, occurs as a glucoside in *Erysimum perowskianum.*

Glycotropaeolin, $C_{14}H_{18}O_9S_2NK$ or $C_6H_5\cdot CH_2\cdot N{:}\overset{\diagup O\cdot SO_3K}{C}{—}S\cdot C_6H_{11}O_5$, has been isolated from *Tropaeolum maius*, *Lepidium sativum*; enzymatic hydrolysis yields benzyl isothiocyanate $C_6H_5\cdot CH_2\cdot N{:}C{:}S$, glucose and $KHSO_4$, while $AgNO_3$ gives the Ag salt of *tropaeolic acid,* $C_6H_5\cdot CH_2\cdot N{:}\overset{\diagup O\cdot SO_3Ag}{C}{—}SAg$ (*Gadamer*, Ber. **32**, 2335).

Sinalbin, $C_{30}H_{42}O_{15}S_2N_2\cdot 5H_2O$ or



$$(p)(HO)\cdot C_6H_4\cdot CH_2\cdot N{:}C\begin{array}{l}\diagup O\cdot SO_3[N(CH_3)_3\cdot CH_2\cdot CH_2\cdot OOC\cdot CH{:}CH\cdot C_6H_2(OCH_3)_2(OH)]\\ \diagdown S\cdot C_6H_{11}O_5\end{array},$$

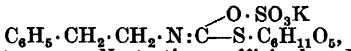
m.p. 84°, anhyd. 140°, $[\alpha]_D$ — 8°, is found in the seeds of the white mustard (*Sinapis alba*). It is hydrolysed by myrosinase into glucose, sinalbin mustard oil $p\text{-}(HO)C_6H_4.CH_2.N{:}C{:}S$, and *sinapin sulphate*

$$(HO)(CH_3O)_2C_6H_2\cdot CH{=}CH\cdot COO\cdot CH_2\cdot CH_2\cdot N(CH_3)_3[SO_4H],$$

m.p. 188°; sinapin decomposes readily into choline and sinapic acid

$$(HO)(CH_3O)_2C_6H_2\cdot CH{:}CH\cdot COOH$$

(*Gadamer*, Ber. **30**, 2327).

Glyconasturtiin, $C_{15}H_{20}O_9S_2NK$ or  $C_6H_5\cdot CH_2\cdot CH_2\cdot N{:}\overset{O\cdot SO_3K}{C}{-}S\cdot C_6H_{11}O_5$, is prepared from the seeds of the watercress *Nasturtium officinale.* Its constitution as the glucoside of phenylethyl isothiocyanate has been proved in the usual way by fission with myrosinase and with $AgNO_3$ (*Gadamer*, Ber. **32**, 2335).

For the synthesis of mustard oil glucosides from the silver salts of thiourethanes and acetobromoglucose, see *Schneider, Clibbens, Hüllweck* and *Steibelt*, Ber. **47**, 1258.

Finally, mention will be made here of the acid potassium salt of the nitrogen-free tribasic **atractylic acid** (carlinic acid) $C_{30}H_{48}O_{18}S_2K_2$, m.p. 173°, $[\alpha]_D$ — 64·4°. This is prepared from the poisonous roots of the thistle *Atractylis gummifera* (*Carlina gummifera*), which occurs in Mediterranean countries (*Pitini*, Arch. Farm. sperim. **29** (1920), 88). Complete acid hydrolysis of the glucoside gives an aglucone $C_{14}H_{22}O_4$, which has not been investigated further, 2 mol. valeric acid $C_5H_{10}O_2$, 2 mol. $KHSO_4$, and glucose (*Wunschendorff* and *Braudel*, Bull. Soc. Chim. biol. **13** (1931), 758, 764). With KOH, atractylic acid gives at first potassium valerate $C_4H_9{\cdot}COOK$, while continued hydrolysis yields β-atractylic acid and $KHSO_4$. The atractylin formed is converted by dilute acids into glucose and a dihydroxymonocarboxylic acid, atractyligenin $C_{14}H_{22}O_4$, m.p. 168°, not yet identified (*Angelico*, Gazz. **36** (1906), II, 636; **40** (1910), I, 403; *Tocco*, C. 1922 III 292; 1923 III 576, 577). The following is given as a tentative formula (*Ajello*, Gazz. **63** (1933), 289; *Wunschendorff* and *Valier*, Bull. Soc. Chim. biol. **16**, 74, 80; *Ajello*, Gazz. **64** (1934), 59):

$$HOOC(HO)C_{13}H_{19}\cdot O\cdot C_6H_7O_4(OH)_2(COC_4H_9)_2(SO_3K)_2.$$

Nitrogenous derivatives of sugars occur in nature in three classes of organic compounds which are important for vital processes, in the carbohydrate chitin, which has a large molecular weight and forms the shells of *Crustaceae*, in the glycoproteins and nucleoproteins, which are constituents of certain proteins, and as a constituent of the cerebrosides of the brain and nerve substances.

Chitin has been observed in the cell-membranes of fungi (*Gilson*, Ber. **28**, 821; *Scholl*, Mo. **29**, 1023) and of various bacteria (*Biochem.* J. **26** (1932), 1934, 1946). It is found in the horny wings of insects, e.g., the cockchafer. A useful source of this substance is found in the shells of *Crustaceae*, such as the lobster and crab (*Ledderhose*, Ber. **9**, 1200). For the proof of the identity of plant and animal chitin, see *Zechmeister* and *Tóth*, Z. physiol. Chem. **223**, 53; *Diehl* and *van Iterson*, Kolloid-Z. **73** (1925), 142; *Diehl*, Chem. Weekblad **33** (1936), 36; *van Iterson, Meyer* and *Lotmar*, Rec. **55**, 61. With supersaturated HCl in the cold chitin is converted into an amorphous chitodextrin of smaller chain-length (*Zechmeister, Grassmann, Tóth* and *Bender*, Ber. **65**, 1706); hydrolysis with cold conc. HCl followed by mild acetylation, however, or direct acetolysis, yields a crystalline *chitobiose-octacetate* $C_{28}H_{40}O_{17}N_2$, with a 1:4-oxide structure, together with acetates of higher molecular weight such as chitotriose-undecacetate $C_{40}H_{57}O_{24}N_3$ (*Zechmeister* and *Tóth*, Ber. **64**, 2028; *Bergmann, Zervas* and *Silberkweit*, ibid. 2436; N. **19**, 20; *Zechmeister* and *Tóth*, Ber. **65**, 161). Enzymatic hydrolysis with the ferment from snails gives as first product N-acetylchitosamine, m.p. 190° (*Fránkel* and *Kolly*, Mo. **23**, 123; *Karrer* and *Hofmann*, Helv. **12**, 616; *Karrer* and *François*, ibid. 986; synthesis see *Bergmann* and *Zervas*, Ber. **64**, 975; **65**, 1201), which is hydrolysed by hot conc. HCl to *acetic acid* and *chitosamine* $C_6H_{13}O_5N$ (*Tiemann*, Ber. **17**, 241; *Neuberg*, Biochem. Z. **48**, 501). The identification of the latter as an α-amino-sugar was carried out both by the preparation of the corresponding pyrazine (*de Bruyn* and *van Ekenstein*, Rec. **18** (1899), 77) and iminazole derivatives (*Neuberg* and *Wolff*, Ber. **34**, 3840), and also by its conversion into *α-amino-caproic acid* (*Neuberg*, Ber. **35**, 4009; *Bergmann*, *Zervas* and *Silberkweit*, Ber. **64**, 2428) via glucosaminic acid (*Fischer* and *Tiemann*, Ber. **27**, 138; *Fischer* and *Leuchs*, Ber. **35**, 3787). That its configuration corresponds to that of glucose follows from the formation of a quaternary trimethylamine salt (*F. Micheel* and *H. Micheel*, Ber. **65**, 253), and the detection of *d*-glucosazone, m.p. 211°, as the chief product of the deamination of chitosamine (*Tiemann*, Ber. **19**, 50; *Zechmeister* and *Tóth*, Ber. **66**, 522). Chitin can also be degraded by an enzyme complex present in extracts of fungi (*Grassmann*, *Zechmeister*, *Tóth* and *Stadler*, Ann. **503**, 174) and in the emulsion of bitter almonds (*Zechmeister*, etc., Ber. **65**, 1706; *Helferich* and *Winkler*, Z. physiol. Chem. **209**, 269), which consists of a chitinase and a β-glucosidase (*Grassmann*, *Zechmeister*, *Bender* and *Tóth*, Ber. **67**, 1). According to one view, the molecule of chitin is based upon the unit ($C_{30}H_{50}O_{19}N_4$) which is composed of 3 mols. of acetylamino-glucose and 1 mol. of aminoglucose (*Irvine*, J. **95**, 564; *Irvine* and *Hynd*, J. **105**, 698); the way in which the amino-sugar molecules are joined to each other is not yet fully understood. As chitin has no reducing properties, while the whole molecule is destroyed by the action of nitrous acid, there is the possibility that the combination involves the amino- and aldehyde-groupings, but this idea is not in agreement with the formation of *chitopyrrole* (1-n-hexyl-2-methyl-pyrrole) $C_{11}H_{19}N$, in the distillation of chitin with Zn dust (*Karrer* and *Smirnoff*, Helv. **5**, 832). An X-ray comparison of chitin and cellulose indicates the 1:4-structure and the presence of the β-glucosidic link (*Meyer* and *Mark*, Ber. **61**, 1936).

Lycoperdin, $C_{13}H_{24}O_9N_2$, is obtained from a species of *Lycoperdon*. It reduces Fehling's solution and gives the biuret reaction; its hydrolysis yields 2 mol. glucosamine and 1 mol. *formic acid* (*Kotake* and *Sera*, Z. physiol. Chem. **88**, 56).

The term **glycoproteins**[1] is used to describe a group of proteins composed of a protein and a component which contains an amino-sugar (*Takahata*, Z. physiol. Chem. **136**, 82). The group is sometimes divided into the mucins and the mucoids, the former being precipitated by acids and the latter soluble in them. The hydrolysis of the glycoproteins is best carried out by digestion with pepsin. From the chemical point of view, the glycoproteins can be divided into two groups, which yield on hydrolysis a protein and

(a) chondroitin- or mucoitin-sulphuric acid, or

(b) a sulphur-free amino-sugar component.

The synthesis of glycopeptides has been carried out by the condensation of aceto-halogeno-sugars with esters of amino-acids or with peptides (*Maurer* and *Schiedt*, Z. physiol. Chem. **206**, 125), and by the reaction of O-acylated amino-sugars with N-carbobenzoxy-amino-acid chlorides (*Bergmann* and *Zervas*, Ber. **64**, 975; **65**, 1201) or with azido-fatty acid halides (*Bertho*, *Holder*, *Meiser* and *Huther*, Ann. **485**, 127; *Bertho* and *Maier*, Ann. **495**, 113; Z. physiol. Chem. **222**, 139).

Chondroitin-sulphuric acid, $C_{28}H_{44}O_{29}S_2N_2$ or $C_{34}H_{54}O_{34}S_2N_2$, is obtained from the chondromucoid of cartilage, sinew and bone, and is decomposed by complete hydrolysis with dilute acids into chondrosamine (isomeric with chitosamine), glucuronic acid, acetic acid and sulphuric acid (J. Biol. Chem.

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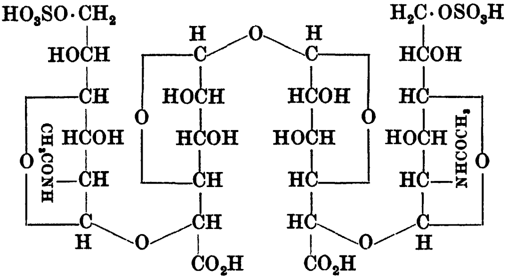
[1] *P. A. Levene*, Hexosamines and Mucoproteins, London 1925. — *O. Kestner*, Chemie der Eiweisskörper, Brunswick 1925.

86, 105). The sulphuric acid may be removed from the molecule by mild hydrolysis with chondrosulphatase from *Bact. fluorescens* (*Neuberg* and *Hofmann*, N. **19**, 484), the product being chondroitin; the acetate residue can readily be split out from the latter, giving chondrosin $C_{12}H_{21}O_{11}N$; energetic treatment of this yields glucuronic acid and chondrosamine $C_6H_{13}O_5N$ (2-amino-galactose, lyxohexosamine, see *Levene*, Biochem. Z. **124**, 37; J. Biol. Chem. **57**, 337; for its synthesis by the reduction of lyxohexosaminic acid, see *Levene*, J. Biol. Chem. **81**, 609). The following schematic formula has been proposed for chondroitin-sulphuric acid on the evidence of its reactions (*Levene* and *La Forge*, J. Biol. Chem. **20**, 95):



(for the configurations of the galactose and of the glucuronic acid, see vol. I, p. 705 and 716).

Mucoitin-sulphuric acid is obtained from the mucus of the respiratory and digestive organs, from the mucoid of the eyes, from frog and fish spawn and from snail mucus. Its constitution is similar to that of chondroitin-sulphuric acid, but it contains glucosamine as the amino-sugar (*Levene*, J. Biol. Chem. **86**, 105).

Ovomucoid from white of egg (*Mörner*, Z. physiol. Chem. **34**, 207; J. Biol. Chem. **84**, 49, 63) is a sulphur-free glycoproteid of sub-group b (see p. 369); pepsin and HCl hydrolyse it to glucosamine and acetic acid (*Oswald*, Z. physiol. Chem. **68**, 173; *Mörner*, ibid. **80**, 430). Proteins which contain carbohydrates are also found in the egg-sacs of cuttle-fish (*Cephalopodae*) and in the sponge *Chondrosia reniformis*.

Serum protein contains a nitrogenous trisaccharide, composed of 1 mol. glucosamine and 2 mol. mannose (*Rimington*, Biochem. J. **23** (1929), 430; **25** (1931), 1062; *Levene* and *Rothen*, J. Biol. Chem. **84**, 63).

Hyaloidin, $C_{26}H_{46}O_{20}N_2$, from ovarian mucus, is hydrolysed to 2 mol. glucosamine, 2 mol. hexose and acetic acid (*Schmiedeberg*, Arch. Path. Pharm. **87**, 1).

A carbohydrate of high molecular weight, **sinistrin**, which forms galactose on hydrolysis (*May*, C. 1931 I 3695), has been isolated from the proteid of the glands of a vineyard snail and from the mucus of the squill (*Bulbus scillae*) (*Rosenthaler* and *Kohli*, Apoth.-Ztg. **45** (1930), 1097).

Chitosamine can be detected in the hydrolysis product of tussore silk fibroin (*Abderhalden* and *Heyns*, Z. physiol. Chem. **202**, 37).

An important class of nitrogenous and phosphorus-containing glycosides has already been discussed shortly in Vol. I, p. 748; these are the

NUCLEIC ACIDS[1]

They are found free (*Steudel* and *Takahata*, Z. physiol. Chem. **133**, 165) or combined with proteins (histones, protamines, clupein, etc.) as "nucleoproteins" in the nuclei of almost all animal and plant cells (*Kossel*, Z. physiol. Chem **25**, 165; *Ackermann*, ibid. **43**, 299;

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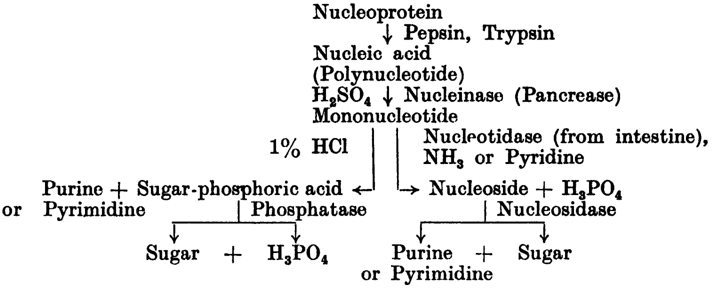
[1] *P. A. Levene* and *L. W. Bass*, Nucleic Acids, Am. Chem. Soc. Monograph, 1931.

Steudel, ibid. **130**, 136), and also in carcinomic tissue and in important glands (thymus, pancreas); they also probably act as carriers for enzymes (e.g. trypsin). In addition they can be isolated from bacteria and fungi (yeast). The wheat germ contains triticonucleic acid.

The mononucleotides, which, combined as esters with the polynucleotides, form the nucleic acids, and which have been found to occur naturally in many tissues (e.g. muscle, yeast, etc.), are in part co-ferments for important enzymatic vital processes (muscle contraction, see *Embden* and *Zimmermann*, Z. physiol. Chem. **167**, 137; *Embden*, *Riebeling* and *Selter*, ibid. **179**, 149; *Lohmann*, N. **19**, 180; alcoholic fermentation, see *Grassmann* and *Mayr*, Z. physiol. Chem. **214**, 184, etc.); they also produce an acceleration in the rate of beating of the heart (*Lautenschläger*, Z. angew. Chem. **46**, 202; *Lindner*, Z. physiol. Chem. **218**, 12).

Fission products of the mononucleotides have also been found in nature, such as sugar derivatives of the pyrimidine and purine series ("nucleosides").

The complete hydrolysis of the nucleic acids yields purines, pyrimidines, sugars (chiefly pentoses) and phosphoric acid. The partial degradation can be represented thus:



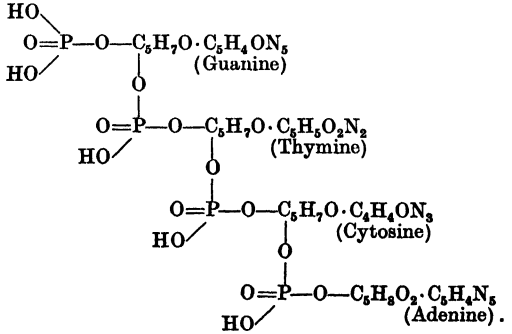
The fact that the nucleotides can yield purine or pyrimidine glycosides and also sugar-phosphoric acids shows that they are built up as follows:

Purine or pyrimidine — sugar — phosphoric acid.

The purines can be removed from the complex much more easily than the pyrimidines (*Steudel*, Z. physiol. Chem. **48**, 425; *Feulgen*, ibid. **102**, 244; see also *Osborne* and *Heyl*, Amer. J. Physiol. **21**, 157; *Jorpes*, C. 1928 II 1343), and it seems highly probable that they are combined with the carbohydrate in the 7-position of the purine nucleus (*H. Fischer*, Z. physiol. Chem. **60**, 69; *Levene* and *Jacobs*, Ber. **44**, 746), while in the pyrimidine the union is through N-atom 3 (*Bredereck*, Z. angew. Chem. **47**, 292). The carbohydrate (for proof of its furanoid structure by means of trityl chloride, see *Bredereck*, Ber. **65**, 1830; **66**, 198; and by hydrolysis of the permethylated complex to 2:3:5-trimethylpentose, see *Levene* and *Tipson*, J. Biol. Chem. **97**, 491) is combined with the base by means of a glucosidic link, since neither the nucleic acids nor the nucleosides have reducing properties. Thymine (5-methyluracil, vol. I, 628) seems to be a specific component for the animal organism; the absence of cytosine (2-hydroxy-6-aminopyrimidine, vol. I, 628) is characteristic of carcinomic tissue. The distinction between plant and animal nucleotides possibly arises from a different type of combination of the pentose and phosphoric acids: the former yield 60—75$^0/_0$ of furfural, the latter only 8—11$^0/_0$ (*Embden* and *Schmidt*, Z. physiol. Chem. **181**, 130; *Steudel* and *Wohinz*, ibid. **200**, 82; *Steudel*, ibid. **216**, 77). In the tetranucleotides (e.g. yeast- and thymus-nucleic acids), the formation of two diphosphoric acid nucleosides as fission products, and the electrometric titration results (*Levene* and *Simms*, J. Biol. Chem. **70** (1926), 327) indicate that the four nucleotides are combined through three of their phosphoric acid residues; and from the velocity of hydrolysis it can be seen that the phosphoric acid is attached to a secondary hydroxyl group of the sugar (*Levene* and *Jorpes*, J. Biol. Chem. **81** (1929), 575).

For a determination of the molecular size of the nucleic acids and nucleotides by the diffusion method, see *Myrbäck* and *Jorpes*, Z. physiol. Chem. **237**, 159.

Thymus nucleic acid, $C_{39}H_{51}O_{25}N_{15}P_4$, is found in several other organs and tissues besides the thymus. The formation of four different bases (guanine, adenine, thymine and cytosine) in equimolecular quantities as the result of complete acid hydrolysis indicates a tetranucleotidic structure (*Steudel*, Z. physiol. Chem. **49**, 406; *Levene* and *Mandel*, Biochem. Z. **10**, 215); this has been confirmed by the less vigorous methods of degradation which have been developed. Fission by the picric acid method (*Thannhauser* and *Ottenstein*, Z. physiol. Chem. **114**, 39; *Thannhauser* and *Blanco*, ibid. **161**, (1926), 126) yields guanine and adenine picrates; uridine- and cytidine-diphosphoric acids were isolated as brucine salts. Hydrolysis with the secretion from the small intestine of the dog gives the nucleosides of guanine, adenine or hypoxanthine, thymine and cytosine (J. Biol. Chem. **81**, 711; **83**, 793; **88**, 753; **96**, 461; *Thannhauser* and *Angermann*, Z. physiol. Chem. **186**, 13; **189**, 174; *Bielschowsky* and *Klein*, ibid. **207**, 202; *Klein*, ibid. **224**, 244); if the phosphatase action is stopped by the addition of phosphate and arsenate, the ferment "thymonucleinase" from the mucus of the walls of the intestine can depolymerise the nucleic acid to the corresponding mononucleotides (*Klein*, ibid. **207**, 125; **218**, 164; *Klein* and *Thannhauser*, ibid. **218**, 173; **224**, 252). The carbohydrate of thymus nucleic acid, thymnose $C_5H_{10}O_4$, has been identified as 2-desoxy-ribose (*Levene*, *Mikeska* and *Mori*, J. Biol. Chem. **85**, 785). The results of these investigations can be summarised in the following formula for the nucleic acid:


HO
O=P—O—$C_5H_7O·C_5H_4ON_5$
HO
(Guanine)
O
O=P—O—$C_5H_7O·C_5H_5O_2N_2$
HO
(Thymine)
O
O=P—O—$C_5H_7O·C_4H_4ON_3$
HO
(Cytosine)
O
O=P—O—$C_5H_8O_2·C_5H_4N_5$
HO
(Adenine).

A ring-structure for the tetranucleotide has been suggested on the grounds of the titration results (*Klein* and *Rossi*, Z. physiol. Chem. **231**, 104; *Makino*, ibid. **232**, 229; **236**, 201).

The **nucleic acid of carcinomic tissue** is decomposed by caustic soda into two nucleotides $C_{48}H_{64}O_{32}N_{10}P_2$ and $C_{36}H_{45}O_{23}N_7P_2$; the former yields guanine and adenine, the latter guanine and thymine. Cytosine, which is present in normal animal tissue, is not found in the hydrolysis product (*Willheim*, Biochem. Z. **168** (1925), 488; *Sokoloff*, Compt. rend. Soc. Biol. **101** (1929), 888).

From **pancreas-nucleoprotein** a nucleotide can be prepared which consists of 1 mol. of thymus nucleic acid and 2 mol. of guanylic acid $C_{10}H_{14}O_8N_5P$ (guanine-ribose-phosphoric acid), m.p. 180°, $[\alpha]_D - 7{\cdot}5°$ (*Steudel*, Z. physiol. Chem. **53**, 539; *Steudel* and *Brigl*, ibid. **68**, 40; *Steudel* and *Nakagawa*, ibid. **126**, 250; *Jorpes*, Biochem. Z. **151**, 227; C. 1928 II 1343). For its formulation as a pentanucleotide, see *Jorpes*, Biochem. J. **28** (1934), 2102; cf. *Myrbäck* and *Jorpes*, Z. physiol. Chem. **237**, 159.

A **hexose-nucleic acid from chicken embryos** is described by *Calvery*, J. biol. Chem. **77**, 489.

Tuberculinic acid, the nucleic acid of the tubercle bacillus (*Ruppel*, Z. physiol. Chem. **26**, 218), is also of the animal acid type, since it contains thymine. The bases isolated are guanine, adenine, cytosine and 5-methylcytosine (*Johnson* and *Coghill*, Am. **47**, 2838); the nucleic acid contains a hexose (*Brown* and *Johnson*, ibid. **45**, 1823).

Diphtheria-toxin has also been considered to be a nucleoprotein (*Leulier*, *Sedallian* and *Gaumont*, Compt. rend. Soc. Biol. **97** (1927), 1543); it contains the fission products of animal nucleic acids (*Coghill* and *Barnes*, Anal. Fis. Quím. **30** (1932), 208).

The nucleic acid of the **nitrogen-fixing bacteria** yields phosphoric acid and carbohydrate, and adenine, guanine and pyrimidine bases (*Mockeridge*, Biochem. J. **18** (1924), 550).

The **nucleic acid** of the **timothy-grass-bacteria** has been found to give as fission products adenine, guanine, uracil, cytosine, a pentose and phosphoric acid (*Coghill*, J. Biol. Chem. **90**, 57).

Yeast nucleic acid, $C_{38}H_{49}O_{29}N_{15}P_4$, gives on energetic hydrolysis the bases adenine, guanine, cytosine and uracil, 4 mol. *d*-ribose and 4 mol. phosphoric acid, and also the nucleotides and nucleosides of cytosine and uracil (*Levene* and *Jacobs*, Ber. **42**, 1198; 2473; **44**, 1027; J. Biol. Chem. **41**, 19; **43**, 379; *Calvery* and *Jones*, J. Biol. Chem. **73**, 73). The milder methods of hydrolysis with ammonia or enzymes, which only attack the phosphoric anhydride bonds, gives 1 mol. of uridine-phosphoric acid, $C_9H_{13}O_9N_2P$, m.p. 202°, $[\alpha]_D + 10{\cdot}5°$, and 2 mols. of triphospho-nucleic acid $C_{29}H_{38}O_{21}N_{13}P_3$ (*Thannhauser* and *Sachs*, Z. physiol. Chem. **109**, 177; **112**, 187); the latter is decomposed by fission with picric acid into the picrates of guanine and adenine, phosphoric acid and cytidine-phosphoric acid $C_9H_{14}O_8N_3P$, m.p. 233° (dec.), $[\alpha]_D + 40°$ (*Thannhauser*, ibid. **131**, 296; *Steudel* and *Takahata*, ibid. **133**, 165; *Levene* and *Jacobs*, Ber. **42**, 2474, 2703). In contrast to thymus nucleic acid, yeast nucleic acid is readily split by dilute alkali into mononucleotides of the above bases. The carbohydrate of the nucleic acid, *d*-ribose, has the furanose structure (*Bredereck*, Z. physiol. Chem. **223**, 61). The phosphoric acid residue of cytidine- and uridine-phosphoric acids is placed, by analogy, upon C-atom 3 of the ribose, because the mononucleotides give trityl compounds and do not increase the conductivity of boric acid (*Bredereck*, ibid. **224**, 79). For a tentative formula which is analogous to that of thymus nucleic acid (see p. 372), and is based on titration results, see *Levene* and *Sims*, J. Biol. Chem. **70**, 332; *Makino*, Z. physiol. Chem. **236**, 201.

A **nucleic acid** from the mycelium of *Aspergillus Oryzae* contains, as basic constituents, guanine, adenine, hypoxanthine (?) and uracil (*Takata*, J. Soc. Chem. Ind. Japan (suppl.) **32** (1929), 245).

The **tritico-nucleic acid** from wheat germ yields the same basic components as yeast nucleic acid (*Osborne* and *Harris*, Z. physiol. Chem. **36**, 85; *Feulgen* and *Rosenbeck*, ibid. **135**, 203; *Levene* and *La Forge*, Ber. **43**, 3164; J. Biol. Chem. **31**, 295; *Calvery* and *Remsen*, ibid. **73** (1927), 593).

The **adenosine-triphosphoric acid,** $C_{10}H_{16}O_{13}N_5P_3$, of muscle (*Lohmann*, N. **17**, 624; *Lohmann* and *Schuster*, Biochem. Z. **282**, 104), of yeast (*Wagner-Jauregg*, Z. physiol. Chem. **238**, 129), and of protoplasm is decomposed by the enzymes of alkaline muscle extract into adenylic acid, which accompanies it in animal tissues, and 2 mol. of phosphoric acid (*Mozolowski*, *Reis* and *Sobczuk*, Biochem. Z. **249**, 157; *Lohmann*, ibid. **282**, 109). In an aqueous medium, however, the fission of ammonia takes place more rapidly than that of phosphoric acid, and hence inosine-triphosphoric acid can be isolated (*Lohmann*, Biochem. Z. **254**, 381); this is decomposed further by energetic treatment into inosic acid and 2 mol. of phosphoric acid (*Schmidt*, Z. physiol. Chem. **179**, 280; *Meyerhof* and *Lohmann*, Biochem. Z. **253**, 431). The nucleotide, which still has the free amino-group of adenine and four titratable hydroxyl-groups (*Lohmann*, Biochem. Z. **254**, 381; **282**, 120), must be assumed to contain a pyrophosphate-complex which can be hydrolysed easily, in addition to the firmly combined orthophosphoric acid; this conclusion is supported by the occurrence of pyrophosphate in muscle and in the products obtained by weakly alkaline hydrolysis (*Lohmann*, N. **16**, 298; **17**, 624; Biochem. Z. **202**, 466; **203**, 164). The sugar component is probably a pentose. The acid can be determined quantitatively by treatment with hot HCl, and determination of the readily hydrolysable phosphoric acid (2 mol.) and of the pentose (*Ferdmann*, Z. physiol. Chem. **216**, 205).

Adenyl-pyrophosphoric acid must be considered as the forerunner of adenylic acid in animals, and plays an important part as a co-enzyme in the formation of lactic acid in the muscle (*Lohmann*, N. **19**, 180; Biochem. Z. **271**, 564; *Ostern* and *Baranowski*, ibid. **281**, 157; *Meyerhof* and *Kiessling*, ibid. **283**, 83), and in the phosphorylation process which takes place in alcoholic fermentation (idem, ibid. **267**, 313; *Lutwak-Mann* and *Mann*, ibid. **281**, 140).

Adenylic acid, $C_{10}H_{14}O_7N_5P \cdot H_2O$, occurs in nature in two isomeric forms, (t) and (h), which differ but little in their physical constants (m.p., rotation and solubility); in chemical properties, however, such as complex formation, deamination (for the significance of this in muscle metabolism see *Embden*, etc., Z. physiol. Chem. **179**, 149–237), hydrolysis and behaviour on distillation with acid, they show marked differences. t-Adenylic acid is ten times as strong as h-adenylic acid in its physiological action upon the heart of the guinea-pig (*Lindner*, ibid. **218**, 12).

t-Adenylic acid (adenine-furanoriboside-5-phosphoric acid), m.p. 195°, $[\alpha]_D$ —37·9°, first obtained from muscle tissue (*Embden* and *Zimmermann*, ibid. **167**, 136; *Klimek* and *Parnas*, Biochem. Z. **252**, 392; *Ostern*, ibid. **254**, 65) and later from yeast (*Lindner*, Z. physiol. Chem. **218**, 12), loses phosphoric acid on hydrolysis much more slowly than the h-acid, and when distilled with acids gives a distinctly lower yield of furfural (*Steudel*, ibid. **216**, 77). Since it gives a complex Cu salt, there must be two adjacent hydroxyls remaining in the ribose molecule; hence the phosphoric acid is attached to the sugar in the 5-position (*Klimek* and *Parnas*, Biochem. Z. **252**, 392; *Steudel*, Z. physiol. Chem. **216**, 77; *Parnas* and *Klimek*, ibid. **217**, 75); this is also the case for the deamination product of muscle adenylic acid, inosic acid (*Levene* and *Jacobs*, Ber. **41**, 2703; **42**, 335; *Levene* and *Harris*, J. Biol. Chem. **95**, 755).

h-Adenylic acid (adenine-furanoriboside-3-phosphoric acid), m.p. 195°, $[\alpha]_D$ —40·5°, from the hydrolysis product of yeast (*Steudel* and *Peiser*, Z. physiol. Chem. **127**, 265; *Steudel*, ibid. **216**, 77), tea-leaves (*Calvery*, J. Biol. Chem. **68**, 593), and also from pancreas nucleotide (*Lindner*, Z. physiol. Chem. **218**, 12), is not attacked by deaminase, in distinction to the t-form (*Embden* and *Schmidt*, ibid. **181**, 130). By analogy, the phosphoric acid should be attached to the ribose in the 3-position, since the guanylic acid from yeast nucleic acid has been clearly identified as guanine-furanoriboside-3-phosphoric acid (*Levene* and *Harris*, J. Biol. Chem. **98** (1932), 9). In support of this, the deamination of h-adenylic acid with nitrous acid, followed by hydrolysis, yields *d*-ribose-3-phosphoric acid (idem, ibid. **101**, 419).

It is important to note that the pure co-enzyme of alcoholic fermentation isolated from yeast (*Harden* and *Young*, Proc. Roy. Soc. B, **77**, 405; *v. Euler*, Z. angew. Chem. **44**, 583; *v. Euler*, *Myrbäck* and *Nilsson*, Z. physiol. Chem. **168**, 177; *v. Euler* and *Myrbäck*, ibid. **199**, 189; *v. Euler*, *Myrbäck* and *Hellström*, ibid. **212**, 7), and the co-enzyme of the lactic acid oxidation in the heart-muscle (*Szent-Györgyi*, Biochem. Z. **157**, 50; *Banga* and *Szent-Györgyi*, Z. physiol. Chem. **217**, 39), contain, as chief components, t-adenylic acid (*Kraut* and *Borkowsky*, ibid. **220**, 173; *Andersson*, ibid. **225**, 57; *Myrbäck*, ibid. 125; 199; *Myrbäck* and *Larsson*, ibid. 131) and nicotinic amide (*Warburg*, *Christian* and *Griesse* Biochem. Z. **282**, 157; *Warburg* and *Christian*, ibid. **285**, 156). (Proof of the 5-position of the phosphoric acid residue in the pentose molecule by the action of HIO_4 is given by *v. Euler*, *Karrer* and *Becker*, Helv. **19**, 1060.) Consequently, the loss of phosphoric acid under the action of enzymes runs parallel with the inactivation of the co-zymase (*Myrbäck*; Z. physiol. Chem. **217**, 249). The ultra-violet absorptions of the co-enzymes show very marked resemblances to those of the nucleotides under discussion (*Myrback*, *v. Euler* and *Hellström*, ibid. **214**, 184).

Inosic acid (hypoxanthine-ribose-5-phosphoric acid), $C_{10}H_{13}O_8N_4P$, is found in muscle and can be prepared from meat extract (*Liebig*, Ann. **62**, 257; *Haiser* and *Wenzel*, Mo. **30**, 377; *Levene* and *Jacobs*, Ber. **44**, 746; Biochem. Z. **28**, 127; *Steudel*, Z. physiol. Chem. **211**, 253). It can be synthesised from monoacetone-inosine and $POCl_3$ (*Levene* and *Tipson*, J. Biol. Chem. **111** (1935), 313).

For **guanylic acid,** $C_{10}H_{14}O_8N_5P \cdot 2H_2O$, m.p. 180°, from the pancreas, see *Levene*, J. Biol. Chem. **41**, 483; *Hammarsten*, Z. physiol. Chem. **109**, 141; *Feulgen*, ibid. **111**, 257; *Hammarsten* and *Jorpes*, ibid. **118**, 224; from the thymus, see *Feulgen*, ibid. **108**, 147; *Steudel* and *Peiser*, ibid. **120**, 292.

The nucleosides, which are purine- or pyrimidine-sugar compounds, occur in nature as well as the nucleic acids:

Vernine, $C_{10}H_{13}O_5N_5$, m.p. 240°, $[\alpha]_D$ —60·4°, a nucleoside from the young plants of *Vicia*, *Lupinus* and *Cucurbita*, has been shown to be a guanine-d-riboside (*Schulz* and *Trier*, ibid. **70**, 143; *Steudel* and *Freise*, ibid. **120**, 126; *Bredereck*, ibid. **223**, 61).

The seeds of *Croton tiglium* contain the isomeric **crotonoside,**

$$C_{10}H_{13}O_5N_5 \cdot 2H_2O,$$

m.p. 248° (decomp.), $[\alpha]_D$ —60·38° (NaOH), which can be hydrolysed to isoguanine (2-hydroxy-6-amino-purine) and *d*-ribose (*Cherbuliez* and *Bernhard*, Helv. **15**, 464, 978).

Adenosine, $C_{10}H_{13}O_4N_5 \cdot 1^1/_2H_2O$ (adenine-riboside), $[\alpha]_D$ —60°, has been isolated from heart muscle (*Szent-Györgyi* and *Drury*, J. Physiol. **67** (1929), 35); *Bredereck*, Z. physiol. Chem. **223**, 61).

Inosine (carnine), $C_{10}H_{12}O_5N_4$, m.p. 218°, $[\alpha]_D$ —72·9°, from meat-extract, yeast and sugar-beet, is hypoxanthine-riboside (*Haiser* and *Wenzel*, Mo. **29**, 157; *Levene* and *Jacobs*, Ber. **41**, 2703; **42**, 335; 1198; *Bredereck*, loc. cit.)

Vicine, $C_{10}H_{16}O_7N_4 \cdot H_2O$ (1-glucosido-4:6-dihydroxy-2:5-diamino-pyrimidine), m.p. 242°, $[\alpha]_D$ — 8·77°, from the seeds of *Vicia fabia* and *sativa* (common vetch), is decomposed by boiling with dilute acids into *divicine* $C_4H_6O_2N_4$ (4:6-dihydroxy-2:5-diamino-pyrimidine), *ammonia* and glucose (*Winterstein*, Z. physiol. Chem. **105**, 258; *Johnson* and *Johns*, Am. **36**, 545; *Fischer*, Ber. **47**, 2611; *Levene* and *Senior*, J. Biol. Chem. **25** (1916), 607; *Thannhauser* and *Dorfmüller*, Ber. **47**, 1304). The paralytic disease known as "lathyrismus", which occurs among the natives of India and the Mediterranean countries, is due to their habit of eating *Vicia sativa*, i.e. divicine, as part of their vegetable diet (*Anderson*, *Howard* and *Simonsen*, Nature **116** (1925), 260).

In the older plants is found **convicine,** $C_{10}H_{15}O_8N_3 \cdot H_2O$, decomp. 287° (*Ritthausen* and *Preuss*, J. **59**, 487; *Ritthausen*, Ber. **29**, 2106; J. pr. **59**, 480; *Johnson*, Am. **56**, 337), which is hydrolysed to *alloxantine*, $C_8H_6O_8N_4$, *ammonia* and glucose (*Fisher* and *Johnson*, Am. **54**, 2038).

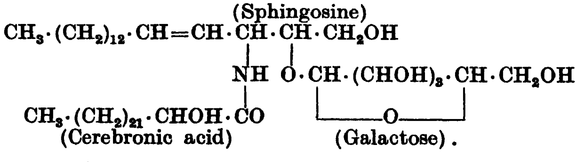
The following *syntheses* have been carried out: pyrimidine-glucoside has been obtained by the interaction of 2:6-dimethoxy-pyrimidine with aceto-bromoglucose; hydrolysis with HCl yielded 3-glucosido-uracil $C_{10}H_{14}O_7N_2$, m.p. 209° (decomp.), $[\alpha]_D + 21{\cdot}4°$ (*Schmidt-Nickels* and *Johnson*, Am. **52**, 4511); for the analogous synthesis of 2- or 6-xylosido-uracil, see *Levene* and *Sobotka*, J. Biol. Chem. **65** (1925), 469; *Hahn*, *Laves* and *Schäfer*, Z. Biol. **84**, 411; *Hahn* and *Laves*, ibid. **85**, 280).

The action of 1-bromo-3:4:6-tribenzoyl-d-glucodesose upon theophylline-silver, followed by debenzoylation, yields theophylline-d-glucodesoside $C_{13}H_{18}O_6N_4$, m.p. 258°, $[\alpha]_D - 26{\cdot}9°$ (see *Levene* and *Cortese*, J. biol. Chem. **92**, 53). For analogous syntheses of theophylline-glucoside and -rhamnoside, see *Fischer* and *Helferich*, Ber. **47**, 210; *Fischer* and *v. Fodor*, ibid. 1058; *Fischer*, ibid., 1390; *Helferich* and *von Kühlewein*, ibid. **53**, 17; of 7-theophylline-xyloside and -riboside, see *Levene* and *Sobotka*, J. Biol. Chem. **65** (1930), 469; adenine-*d*-glucoside and hypoxanthine-*d*-glucoside can be synthesized by similar methods.

The synthesis of a simple nucleic acid has been accomplished from theophylline-*d*-glucoside and $POCl_3$ at —20° in pyridine (*Fischer*, Ber. **47**, 3197).

The **cerebrosides**[1], found chiefly in the brain- and nerve-tissues, are compounds of the amide type derived from *sphingosine-galactoside* (psychosine) and a *fatty acid* or *hydroxy-acid* of the C_{24}-series. Their fission with sulphuric and acetic acids leads to galactose and a fatty acid sphingoside (which sometimes occurs free in nature); the latter is hydrolysed by longer treatment with alcoholic sulphuric acid. The treatment of cerebrosides with baryta only breaks the amide link, and gives the fatty acid and sphingosine-galactoside.

Phrenosine (cerebron), $C_{48}H_{93}O_9N\cdot 2H_2O$, m.p. 212°, $[\alpha]_D + 8°$ (in $CHCl_3$), first isolated from the brain (*cerebrum*) by *Thudichum* in 1874, is found also in the nerve-tissues and other organs of mammals, birds and fishes. Its hydrolysis yields cerebronic acid, m.p. 108° (α-hydroxy-lignoceric acid, see *Klenk* and *Diebold*, Z. physiol. Chem. **215**, 79), sphingosine $C_{18}H_{37}O_2N$ (*triacetate* m.p. 100°; ozonolysis to myristic acid and α-amino-β: γ-dihydroxybutyric acid, see idem., ibid. **198**, 25; *Fischer* and *Feldmann*, Ber. **65**, 1211), and galactose, $C_6H_{12}O_6$ (*Thierfelder*, Z. physiol. Chem. **44**, 366; *Klenk*, ibid. **179**, 312). Cerebronic acid is a mixture which consists mainly of α-hydroxy-n-tetracosanic acid, $C_{24}H_{48}O_3$, but X-ray examination shows that the corresponding C_{22} and C_{26} acids are also present (*Chibnall*, Biochem. J. **30** (1936), 100). Partial hydrolysis of the cerebroside with baryta yields psychosine (sphingosine-galactoside, see *Klenk* and *Harle*, ibid. **178**, 221) $C_{24}H_{47}O_7N$, m.p. 215°, and cerebronic acid; partial hydrolysis with sulphuric acid gives cerebronyl-sphingosine $C_{42}H_{83}O_4N$, m.p. 84°, and galactose. A possible constitution for phrenosine is shown in the following formula (*Klenk*, Z. angew. Chem. **44**, 591, but see *Levene* and *Heymann*, J. Biol. Chem. **102** (1933), 1):



$$\begin{array}{l} CH_3\cdot(CH_2)_{12}\cdot CH{=}CH\cdot CH\cdot CH\cdot CH_2OH \\ \qquad\qquad\qquad\qquad\quad NH \quad O\cdot CH\cdot(CHOH)_3\cdot CH\cdot CH_2OH \\ CH_3\cdot(CH_2)_{21}\cdot CHOH\cdot CO \end{array}$$

The compound also occurs in brain tissue as *cerebron-sulphuric* acid, m.p. 210°, which contains a galactose-sulphuric ester (*Blix*, Z. physiol. Chem. **219**, 82).

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[1] *H. Thierfelder* and *F. Klenk*, Die Chemie der Cerebroside und Phosphatide, Berlin 1930.

The free aglycone, cerebronyl-sphingosine (see above), is also present in this tissue (*Klenk*, ibid. **153**, 74).

Cerasine, $C_{48}H_{93}O_8N \cdot H_2O$, m.p. 187°, $[\alpha]_D$ —11·6° (in $CHCl_3$), from the brain, is decomposed by complete hydrolysis into cerasic acid (lignoceric acid) m.p. 85°, which is mainly $C_{24}H_{48}O_2$, but contains also C_{22} and C_{26} acids, sphingosine and galactose (J. biol. Chem. **18**, 477; **26**, 115; *Brigl*, Z. physiol. Chem. **95**, 161). It has been obtained synthetically from galactosido-sphingosine and lignoceryl chloride (*Klenk* and *Harle*, ibid. **189**, 243; *Klenk*, Z. angew. Chem. **48**, 674).

For the presence of lignoceryl-sphingosine, $C_{42}H_{83}O_3N$, m.p. 90°, in pigs' liver, see *Thannhauser* and *Fränkel*, Z. physiol. Chem. **203**, 183; *Fränkel* and *Bielschowsky*, ibid. **213**, 58; in the spleen of cattle, see *Tropp* and *Wiederscheim*, ibid. **222**, 39; and in the lungs of cattle, see *Tropp*, ibid. **237**, 178.

Brain tissue also gives the cerebrosides **nervon,** $C_{48}H_{91}O_8N$, m.p. 180°, $[\alpha]_D$—4·33° (pyridine) (*Klenk*, ibid. **145**, 244), and probably contains **hydroxy-nervon,** $C_{48}H_{91}O_9N$ (*Klenk*, ibid. **157**, 291), though this has not been isolated. They are hydrolysed to sphingosine and galactose, together with *nervonic acid* $C_{24}H_{46}O_2$ or $CH_3 \cdot (CH_2)_7 \cdot CH{:}CH \cdot (CH_2)_{13} \cdot COOH$, cis-form m.p. 39°, the constitution of which is proved by conversion into lignoceric acid (*Klenk*, ibid. **157**, 283), by ozonolysis to pelargonic acid and a dicarboxylic acid $C_{15}H_{28}O_4$, m.p. 114° (*Klenk*, ibid. **166**, 287), and by synthesis from erucyl bromide and sodio-malonic ester (*Hale*, *Lycan* and *Adams*, Am. **52**, 4536), or α-hydroxy-nervonic acid $C_{24}H_{46}O_3$, m.p. 65° which is decomposed by ozone to pelargonic acid and duodecane-1:12-dicarboxylic acid (*Klenk*, Z. physiol. Chem. **174**, 214).

PLANT GLYCOSIDES OF THE HETEROCYCLIC SERIES

(see also the section on nucleic acids)

Indican, $C_{14}H_{17}O_6N \cdot 3H_2O$ (β-indoxyl-glucoside), m.p. 58°, anhyd. 178° (*pentacetate* m.p. 112°), is found in various species of *Indigofera*, in woad (*Isatis tinctoria*), etc. It is decomposed by ferments or acids into glucose and indoxyl, which is rapidly oxidised in the air to indigo blue. The synthesis of the glucoside has been carried out in the following way (see *Robertson*, J. **1927**, 1937; *Robertson* and *Waters*, J. **1933**, 30):

Methyl ester of 3-acetoxy-indole-2-carboxylic acid + acetobromoglucose
↓ NaOH in acetone
Methyl ester of tetracetyl-β-glucosido-3-hydroxy-indole-2-carboxylic acid
↓ hydrolysis
β-Glucosido-3-hydroxy-indole-2-carboxylic acid
↓ acetylation (—CO_2)
1-Acetyl-tetracetyl-β-glucosido-3-hydroxy-indole
(pentacetyl-indican)
↓ NH_3 in CH_3OH
β-Glucosido-3-hydroxy-indole
(indican)

The exact structure of the carbohydrate has been determined by methylation of the natural glucoside: from the hydrolysis of tetramethyl-indican, $[\alpha]_D$ + 9·19°, with methyl alcoholic HCl, indoxyl and 2:3:5:6-tetramethyl-glucose, m.p. 94°, can be isolated; hence the natural product is a derivative of glucofuranose (*Macbeth* and *Pryde*, J. **121**, 1660).

The poisonous **solanum-glycosides** vary in their constitution according to the species of *Solanum* from which they are isolated.

Solanin (t), $C_{45}H_{73}O_{15}N$, $[\alpha]_D$ —59·45°, from the potato, *Solanum tuberosum* (75 g. of solanin from 120 kg. of the eyes of the potato: *Soltys* and *Wallenfels* Ber. **69**, 811), can be acetylated to trideca-acetyl-solanin (t), m.p. 205°;

this can be hydrolysed to bromoacetyl-rhamnosido-galactose and acetyl-solanidin(t)-glucoside, m.p. 115–120°, or to nonoacetyl-solanidin(t)-glucoside-galactoside, m.p. 130°, and tetra-acetyl-rhamnose, m.p. 90° (see *Oddo* and *Caronna*, Gazz. **62** (1932), 1108). Hence it can be deduced that the constituents of the original glycoside are joined in the following manner (idem, Ber. **67**, 446):

Solanidin (t) — *d*-glucose — *d*-galactose — *d*-rhamnose.

The action of dilute acids upon the glucoside leads to the alkaloid solanidin (t) $C_{27}H_{43}ON$, m.p. 219° (*Zemplén* and *Gerecs*, Ber. **61**, 2294; *Bergel* and *Wagner*, Ber. **66**, 1093; *Soltys* and *Wallenfels*, Ber. **69**, 811), which is described among the alkaloids, (Vol. IV).

Solanin (s), $C_{54}H_{96}O_{18}N_2 \cdot H_2O$, $[\alpha]_D$ —58·3°, from *Solanum sodomaeum*, is decomposed by dilute acids into 2 mol. of *solanidin* (s) $C_{18}H_{31}ON$, m.p. 200°, *d*-glucose, *d*-galactose and *d*-rhamnose (*Oddo*, Ber. **62**, 267). The arrangement of the sugars in the molecule is shown by the hydrolysis of deca-acetyl-solanin (s), m.p. 138°, with HBr-acetic acid to hepta-acetyl-solanidin (s)-glucosido-galactoside, m.p. 170°, and bromo-triacetyl-solanidin(s)-rhamnoside, m.p. 132°; it must be as follows (*Oddo* and *Caronna*, Ber. **67**, 446):

Solanidin (s) — *d*-glucose — *d*-galactose — *d*-rhamnose — solanidin (s).

The constitution of the nitrogenous aglycone has not yet been determined.

The green unripe berries of the New Zealand shrub purapura (*Solanum aviculare*) yield the alkaloid glucoside **purapurin**, $C_{48}H_{78}O_{18}N_2$(?), decomp. 220–230°, $[\alpha]_D$—87° (alcohol); its hydrolysis yields sugars and purapuridin $C_{37}H_{57}O_6N_2$(?), which has not been investigated further (*Levi*, Chem. and Ind. **49**, 395 T).

For further nitrogenous glycosides of unknown constitution, see *G. Trier*, Chemie der Pflanzenstoffe, Berlin 1924.

II. THE TANNINS, LICHEN ACIDS, ETC.[1]

The natural tannins are plant products of a phenolic nature which precipitate albuminous substances, such as glue and gelatine, alkaloids, e.g. brucine and caffeine, and many compounds which contain oxygen, e.g. vanillin, with the formation of insoluble molecular compounds. They give salts with the alkali, alkaline earth and heavy metals which are slightly soluble and usually coloured; characteristic colours or precipitates are produced with iron salts, molybdic acid, vanadic acid and other compounds; *Fehling's* solution and gold chloride are usually reduced by tannins. Certain reactions are specific for definite components of a tannin, e.g. the pink colour with KCN for gallic acid; tannins containing a phloroglucinol nucleus are precipitated by bromine-water, colour vanillin-HCl red, and give the pine-shaving reaction; ellagic acid derivatives give a carmine red colour with nitrous acid, which changes to blue or green; pyrocatechol and pyrogallol derivatives colour ferric salts blue or green and give a precipitate with arsenic acid. Pyrocatechol tannins are in particular precipitated by boiling with formaldehyde and HCl.

According to *K. Freudenberg*, the tannins may be divided into two groups:

A. *Hydrolysable tannins* (phenol-glucosides or -esters, and sugar-esters), which are hydrolysed by hot water, dilute acids and alkalis (*Fischer* and *Freudenberg*, Ber. **45**, 925; *Herzig*, Mo. **33**, 846). The fission of the glucoside- or ester-bond is carried out very readily by "tannase", the enzyme from *Aspergillus niger*, a fungus cultivated on myrobalane extract (*Freudenberg* and *Vollbrecht*, Z. physiol. Chem. **116**, 292; *Dyckerhoff* and *Armbruster*, ibid. **219**, 38) (for the hydrolysis, see *Freudenberg* and *Fick*, Ber. **53**, 1733; *Freudenberg* and *Walpuski*, Ber. **54**, 1695; *Freudenberg* and *Vollbrecht*, Ber. **55**, 2420; Ann. **429**, 284; *Freudenberg*, N. 8, 905), and also by "taka-diastase" from *Aspergillus Oryzae* (*Asahina* and *Higuti*, Ber. **66**, 1959). For the depsides (phenol esters), alcoholysis (*Asahina* and *Yanagita*, Ber. **67**, 1966; *Asahina* and *Akagi*, Ber. **68**, 1130) and hydrolysis with HI (method of *Zeisel*) can be used with advantage. The oxidation of the depsides or their bromo-derivatives to the corresponding quinones with bichromate and acetic acid has been used for determining the constitution (*Fuzikawa*, Ber. **68**, 72).

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[1] *K. Freudenberg*, Tannin, Cellulose, Lignin, 2nd Ed. of Chemie der natürl. Gerbstoffe, Springer, Berlin, 1933.

Properties similar to those of the tannins are shown by many aromatic glycosides (see p. 355) and natural colouring matters (see p. 406).

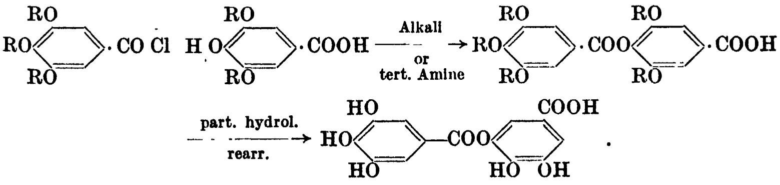
B. *Condensed tannins* (phenol-ketones). With strong alkali these undergo fission at a carbon bond (*Clauser*, Ber. **36**, 105; *Hlasiwetz* and *Pfaundler*, Ann. **127**, 351; *Hlasiwetz*, Ann. **134**, 118).

Some members of this group (such as quinones, benzophenone- and xanthone-pigments, chalkones, the coloured compounds of coto-bark, and of kawa- and curcuma-root) are dealt with under the natural colouring matters.

Besides the acid and alkali fission of the tannins (usually after permethylation or acetylation), the constitutions may be determined in some cases by reduction with Zn and alkali or acid (*Boehm*, Ann. **329**, 269; *Karrer*, Helv. **2**, 466), and by energetic oxidation with conc. HNO_3 (*Einbeck* and *Jabloński*, Ber. **54**, 1086).

The various methods for synthesising the glucosidic link have already been described in the section "glycosides".

The pioneering work in the synthesis of the *depsides* (phenol esters) was that of *Emil Fischer*. He obtained them from the carbomethoxy- or acyl-derivatives of the phenol-carboxylic acids by the following series of reactions (*Fischer* and *Hoesch*, Ann. **391**, 347; *Fischer*, *Bergmann* and *Lipschitz*, Ber. **51**, 45); in the final hydrolysis a rearrangement takes place:



A method which is similar in principle is the synthesis from phenol-carboxylic acid chlorides and aromatic hydroxy-aldehydes: the condensation product, a phenol-ester-aldehyde, is oxidised with permanganate to the phenol-ester acid (depside) (*Currie* and *Russell*, J. **1932**, 2263).

The tannins which are *sugar-esters* are prepared in a similar way, e.g. galloyl-β-glucose from β-tetracetyl-glucose and triacetyl-gallic acid chloride in the presence of quinoline, or from acetobromoglucose and the silver salt of triacetyl-gallic acid (*Fischer* and *Bergmann*, Ber. **51**, 1791). The partial formation of ethers (with diazomethane, dimethyl sulphate or triphenylmethyl chloride), partial acetal formation (with acetone or benzaldehyde) and acylation (with acetic anhydride or benzoyl chloride) make possible the synthesis of partially acylated compounds, and also the introduction of acid residues into various positions of the sugar molecule.

The discovery of the *Hoesch-Houben* phenol-ketone synthesis (*Hoesch*, Ber. **48**, 1122; *Hoesch* and *v. Zarzecki*, Ber. **50**, 462; *Fischer* and *Nouri*, ibid. 611, 693) has been particularly important for the synthetical preparation of condensed tannins.

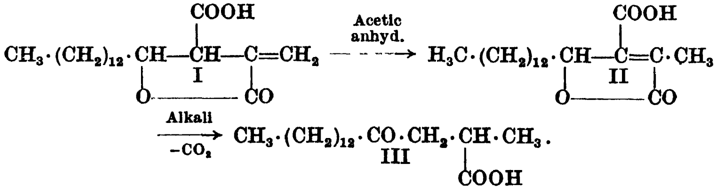
Tanning is used to preserve skins and convert them into leather, and makes them resistant to water and putrefaction. Phenolic compounds, fatty acids, aromatic sulphonic acids (artificial tannins), and also metallic salts (Cr and Al) are used for this purpose. The following technical processes are in use:

Chamois tanning: with fats, fatty acids, to give wash-leather.
Red tanning: with natural tannins, to give Moroccan and Russian leather.
Tanning with artificial tannins, e.g. neradol.
Mineral tanning: with chrome alum, bichromate (chrome leather), or Al sulphate (white tanning for glacé leather).

(a) HYDROLYSABLE TANNINS

(α) DEPSIDES[1]

Proto-lichesteric acid (I), $C_{19}H_{32}O_4$, m.p. 105°, $[\alpha]_D$ —12·7°, from Iceland moss, *Cetraria islandica*, is the only example of an aliphatic compound with an internal depside-like bond. This unsaturated monobasic lactonic acid decolourises permanganate at once, and is catalytically hydrogenated to a dihydro compound $C_{19}H_{34}O_4$, m.p. 101°. The presence of a chain of carbon atoms was shown by oxidation to *myristic acid* $C_{14}H_{28}O_2$, m.p. 54°, and further by reduction with HI and P to α-methyl-α′-n-tetradecyl-succinic acid $C_{19}H_{36}O_4$, m.p. 133–135° (*Asano* and *Azumi*, Ber. **68**, 991), which has been synthesised from propane-ααβ-tricarboxylic ester and tetradecyl iodide (*Asano* and *Ohta*, Ber. **67**, 1842). The terminal position of the double bond was shown by ozonolysis, which yielded formaldehyde, formic acid, oxalic acid and α-hydroxy-pentadecanoic acid $C_{15}H_{30}O_3$, m.p. 92°. Proto-lichesteric acid is a derivative of itaconic acid, and readily undergoes isomeric change in the presence of acetic anhydride to give the corresponding citraconic acid derivative, which is stable to permanganate. This is lichesteric acid (II), m.p. 124°, which can be degraded by alkali via the corresponding β-keto-dicarboxylic acid into lichesterylic acid (III), $C_{18}H_{34}O_3$, m.p. 83° (*Asahina*, J. Pharm. Soc. Japan **1927**, no. 539; *Lehmann*, Z. angew. Chem. **43**, 1117; *Asano* and *Kanematsu*, Ber. **65**, 1175):



$$CH_3\cdot(CH_2)_{12}\cdot\underset{O\text{———}}{CH}—\overset{COOH}{CH}—\underset{\text{———}CO}{C}{=}CH_2 \ \overset{\text{I}}{} \xrightarrow{\text{Acetic anhyd.}} H_3C\cdot(CH_2)_{12}\cdot\underset{O\text{———}}{CH}—\overset{COOH}{C}{=}\underset{\text{———}CO}{C}\cdot CH_3 \ \text{II}$$

$$\xrightarrow[-CO_2]{\text{Alkali}} CH_3\cdot(CH_2)_{12}\cdot CO\cdot CH_2\cdot\underset{COOH}{CH}\cdot CH_3. \ \text{III}$$

The constitution of the latter acid (III) was proved by the Beckmann rearrangement of its oxime to n-tridecylamine $CH_3\cdot(CH_2)_{12}\cdot NH_2$, and α-methyl-succinic acid $HOOC\cdot CH_2\cdot CH(CH_3)\cdot COOH$.

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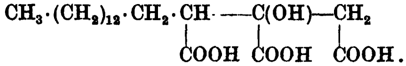
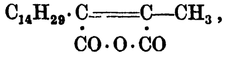
[1] Derived from δέψειν = to tan (*E. Fischer*).

Myristyl-citric acid, nor-caperatic acid



$$CH_3\cdot(CH_2)_{12}\cdot CH_2\cdot \underset{COOH}{CH}—\underset{COOH}{C(OH)}—\underset{COOH}{CH_2}.$$

which is related to protolichesteric acid and lichesteric acid, is also found in nature as its monomethyl ester, **caperatic acid** $C_{21}H_{38}O_7$, m.p. 133·5° (dimethyl ester $C_{23}H_{42}O_7$, m.p. 57·5°), in the Japanese lichen *Parmelia caperata* (*Hesse*, J. pr. **57**, 427). Hydrolysis with alcoholic potash gives nor-caperatic acid and palmitic acid, m.p. 62° (*anilide* m.p. 90·5°). The action of conc. sulphuric acid, which with citric acid leads to acetone, gives in a similar way methyl-pentadecyl-ketone $C_{14}H_{29}\cdot CH_2\cdot CO\cdot CH_3$, m.p. 48° (semicarbazone m.p. 127°). Nor-caperatic acid can also be converted by the action of heat into the corresponding citraconic derivative

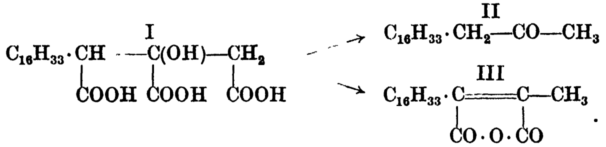


$$C_{14}H_{29}\cdot C{=\!=}C—CH_3,\ \ CO\cdot O\cdot CO$$

with the loss of 1 mol. of water and 1 mol. of CO_2 (*Asano* and *Ohto*, Ber. **66**, 1020).

A higher homologue of nor-caperatic acid is found in the larch fungus *Polyporus off.* and *Fomes off.*; this is **agaricic acid** (I), $C_{22}H_{40}O_7$, m.p. 142° (trimethyl ester m.p. 64°); for its physiological properties, see p. 478.

The oxidative degradation of the acid gives palmitic acid $C_{16}H_{32}O_2$. Being a substituted citric acid (cetyl-citric acid), treatment with conc. sulphuric acid gives a ketone, heptadecyl-methyl-ketone (II), $C_{19}H_{38}O$, m.p. 56°. Its conversion into methyl-hexadecyl-maleic anhydride (III), $C_{21}H_{36}O_3$, m.p. 36°, by the action of heat, corresponds with the change from citric acid to citraconic anhydride (*Siedler*, Ber. **12**, 64; Germ. Pat. 130,073; *Thoms* and *Vogelsang*, Ann. **357**, 145):

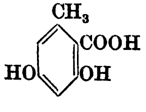


$$\overset{I}{C_{16}H_{33}\cdot \underset{COOH}{CH}—\underset{COOH}{C(OH)}—\underset{COOH}{CH_2}} \rightarrow \overset{II}{C_{16}H_{33}\cdot CH_2—CO—CH_3}$$

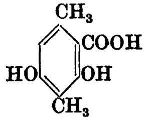
$$\rightarrow \overset{III}{C_{16}H_{33}\cdot C{=\!=}C—CH_3}\ \ \underset{}{CO\cdot O\cdot CO}.$$

Agaricic acid has been reduced to methyl-hexadecyl-succinic acid $C_{21}H_{40}O_4$, m.p. 133·5–135°, which has been synthesised from propane-$\alpha\alpha\beta$-tricarboxylic ester and cetyl iodide (*Asano* and *Ohta*, Ber. **67**, 1842).

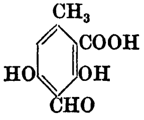
Depsides are derived from certain phenol-carboxylic acids, chiefly those of the orcinol series (and their methyl ethers); the following are the more important of these acids:



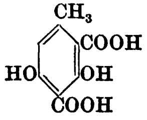
Orsellinic acid



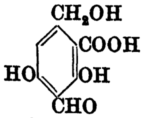
Methyl-orcinol-carboxylic acid



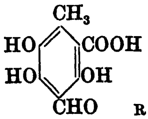
Atranol-carboxylic acid



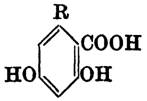
Orcinol-dicarboxylic acid



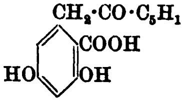
Barbatol-carboxylic acid



Thamnol-carboxylic acid



R = C_3H_7 Divaric acid
R = C_5H_{11} Olivetol-carboxylic acid
R = C_7H_{15} Sphaerophorol-carboxylic acid



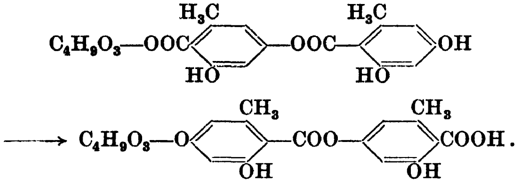
Olivetonic acid

In the depsides the acid components, with the exception of gallic acid and v-pyrogallol-carboxylic acid, are always esterified on the hydroxyl para to the carboxyl group.

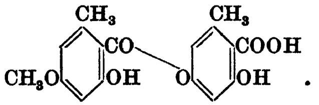
The tannin acids described in the next section, lecanoric acid, erythrin, evernic acid, gyrophoric acid, tenuiorin and umbilicaric acid, contain only orsellinic acid (p. 381) or its methyl ether as components.

Lecanoric acid, *glabratic acid* $C_{16}H_{14}O_7$, white needles, m.p. 166° (*trimethyl ether* $C_{19}H_{20}O_7$, m.p. 148°), the didepside of orsellinic acid, is found in lichens of the genera *Lecanora, Roccella* and *Parmelia.* Mild hydrolysis yields 2 mol. of orsellinic acid $C_8H_8O_4$, m.p. 176°, which by the continued action of alkali is decarboxylated to orcinol $C_7H_8O_2$, m.p. 101° (*Zopf,* Ann. **346,** 98; *Hesse,* J. pr. **83,** 85). Dimethyl-dihydroxy-xanthone is formed by thermal decomposition (*Koller* and *Pfeiffer,* Mo. **62,** 169). For the details of its synthesis from dicarbomethoxy-orsellinic acid chloride and orsellinic acid, see *E. Fischer* and *H. O. Fischer,* Ber. **46,** 1138.

The lichen *Roccella tinctoria* contains **erythrin** $C_{20}H_{22}O_{10}$, m.p. 148°, the erythritol ester of lecanoric acid. Its hydrolysis with boiling water gives at first 1 mol. orsellinic acid and picroerythrin $C_{12}H_{16}O_8$ (the erythritol ester of orsellinic acid), which is decomposed further by baryta into erythritol $C_4H_{10}O_4$ and orsellinic acid or orcinol and CO_2. Treatment of erythrin with hot glacial acetic acid causes an interesting rearrangement to erythric acid (*Hesse,* J. pr. **73,** 136; Ann. **199,** 338):



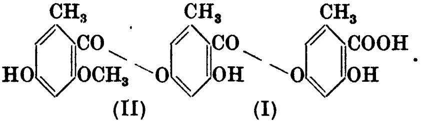
Evernic acid $C_{17}H_{16}O_7$, m.p. 169°, is isolated from *Evernia prunastri* and from oak moss. Its degradation by alkali yields everninic acid $C_9H_{10}O_4$, m.p. 170° (4-methyl ether of orsellinic acid), orcinol and CO_2 (*Zopf,* Ann. **297,** 300; *Fischer* and *Hoesch,* Ann. **391,** 351; *Hesse,* J. pr. **92,** 430; *Walbaum* and *Rosenthal,* Ber. **57,** 770); alkaline hydrolysis of the diethyl ether of the ethyl ester of evernic acid gives the ethyl ether of everninic acid $C_{11}H_{14}O_4$, m.p. 87°, and the ethyl ether of the ethyl ester of orsellinic acid $C_{12}H_{16}O_4$, m.p. 89° (*Robertson* and *Stephenson,* J. **1932,** 1388). Hence evernic acid is the 4-methyl ether of lecanoric acid. The methylation of this lichen acid gives a compound identical with the trimethyl ether of lecanoric acid (*E. Fischer* and *H. O. Fischer,* Ber. **47,** 505). The synthesis of the mothyl ester of evernic acid $C_{18}H_{18}O_7$, m.p. 148°, from acetyl-everninic acid chloride and the methyl ester of orsellinic acid (*Robertson* and *Stephenson,* J. **1932,** 1388), and the synthesis of the methyl ester of diacetyl-evernic acid $C_{22}H_{22}O_9$, m.p. 129°, by partial hydrolysis of triacetyl-lecanoric ester followed by methylation of the diacetyl-lecanoric ester $C_{21}H_{20}O_9$, m.p. 150° (*Koller,* Mo. **61,** 147), confirms this constitution:



Gyrophoric acid, $C_{24}H_{20}O_{10} \cdot H_2O$, m.p. 230° (decomp.), is prepared from various species of *Gyrophora* (*Hesse,* J. pr. **92,** 466; *Zopf,* Ann. **300,** 333). Its constitution as the tridepside of orsellinic acid is shown by molecular weight determinations (*Asahina* and *Watanabe,* Ber. **63,** 3044), and by the syntheses of two of its derivatives, which have been carried out as follows; when the methyl ester of lecanoric acid is condensed with dimethyl-orsellinoyl chloride, methylation of the product gives the methyl ester of gyrophoric acid tetramethyl ether $C_{29}H_{30}O_{10}$, m.p. 197° (*Asahina* and *Kutani*, J. Pharm. Soc. Japan **519** (1925), 1; *Canter, Robertson* and *Waters*, J. **1933**, 493; *Asahina* and *Fuziwaka*, Ber. **65**, 983). Further, partial hydrolysis of triacetyl-lecanoric methyl ester $C_{23}H_{22}O_{10}$, m.p. 157°, and coupling of the product with diacetyl-orsellinoyl chloride gives tetracetyl-gyrophoric methyl ester $C_{33}H_{30}O_{14}$, m.p. 202° (*Koller*, Mo. **61**, 147).

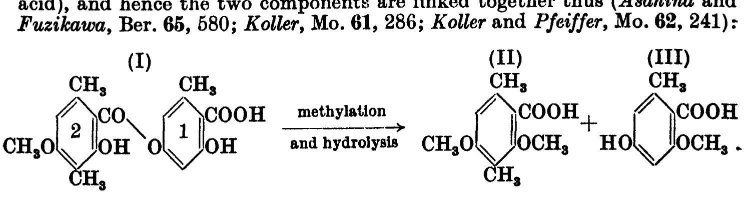
Tenuiorin, $C_{26}H_{24}O_{10}$, m.p. 180°, decomp. 238° (triacetate m.p. 195°), from the pulpy tissue of the lichen *Lobaria pulmonaria tenuior*, is a monomethyl ether of gyrophoric methyl ester, since its trimethyl ether is identical with the tetramethyl ether of gyrophoric methyl ester, m.p. 195°. Tenuiorin is related to gyrophoric acid in the same way as evernic acid to lecanoric acid; this is shown by the hydrolysis of tenuiorin with methyl alcoholic KOH to everninic acid (p. 382), its methyl ester, m.p. 68°, and orsellinic methyl ester, m.p. 137°. Tenuiorin can also be obtained by the partial methylation of gyrophoric acid with diazomethane (*Asahina* and *Yanagita*, Ber. **66**, 1910).

Umbilicaric acid, $C_{25}H_{22}O_{10}$, m.p. 186°, which occurs in many species of *Gyrophora*, is the 2-methyl ether of gyrophoric acid, and is isomeric with the free acid from the previous compound:



Treatment with HI yields *orcinol*, CO_2 and CH_3I, and methylation with diazomethane gives the tetramethyl ether of gyrophoric methyl ester, m.p. 195°, as with tenuiorin. By the action of alkali the molecule may be split either at (I), to give umbilicarinic acid $C_{17}H_{16}O_7$, m.p. 180°, isomeric with evernic acid (*Hesse*, J. pr. **58**, 478; **63**, 545; *Asahina* and *Watanabe*, Ber. **63**, 3044), or at (II), to give lecanoric acid, decomp. 183°, and iso-everninic acid, decomp. 180° (*Koller* and *Pfeiffer*, Mo. **62**, 241). With methanol the molecule is decomposed at the bond (I), yielding iso-everninic methyl ester $C_{18}H_{18}O_7$, m.p. 165°, and orsellinic methyl ester (idem, Mo. **62**, 359).

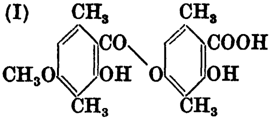
Obtusatic acid, *ramalic acid* (I), $C_{18}H_{18}O_7$, m.p. 203°, from the lichen *Ramalina obtusata*, is also present in the Chinese drug "shi-hoa". It is hydrolysed by alkali to *rhizoninic acid* $C_{10}H_{12}O_4$, m.p. 235° (4-methyl ether of methyl-orcinol-carboxylic acid, cf. p. 381), *orcinol* and CO_2 (from nucleus 1); dimethyl-obtusatic acid gives the methyl ether of rhizoninic acid (II), m.p. 105°, and iso-everninic acid (III), m.p. 114° (2-methyl ether of orsellinic acid), and hence the two components are linked together thus (*Asahina* and *Fuzikawa*, Ber. **65**, 580; *Koller*, Mo. **61**, 286; *Koller* and *Pfeiffer*, Mo. **62**, 241):



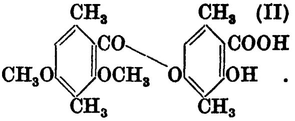
Formula (I) is confirmed by the synthesis of the dimethyl ether of obtusatic methyl ester $C_{21}H_{24}O_7$, m.p. 126°, from the dimethyl ether of methyl-orcinol-carboxylic acid chloride and iso-everninic methyl ester (*Asahina* and *Fuzikawa*, J. pharm. Soc. Japan **53**, 152).

Barbatinic acid (I) and diffractic acid (II), which are partially methylated depsides of methyl-orcinol-carboxylic acid (formula p. 381), have been found in nature:

(I)

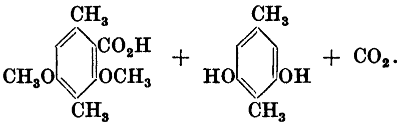


(II)



Barbatinic acid (I), $C_{19}H_{20}O_7$, m.p. 191° (methyl ester m.p. 170°; methyl ether methyl ester m.p. 123°), occurs in *Usnea barbata* and in species of *Cladonia* (*Asahina* and *Fuzikawa*, Ber. **67**, 1793); it is decomposed by dilute baryta into rhizoninic acid (4-methyl ether of methyl-orcinol-carboxylic acid) and methyl-orcinol-carboxylic acid (formula p. 381), $C_9H_{10}O_4$, or methyl-orcinol $C_8H_{10}O_2$, m.p. 163°, and CO_2. The two acids are combined according to the general principles of depside formation (*Stenhouse* and *Groves*, Ann. **208**, 285; *Pfau*, Helv. **9**, 650; **11**, 864, 871). Its methyl ester has been synthesised from acetyl-rhizoninic acid chloride and the methyl ester of methyl-orcinol-carboxylic acid (*Robertson* and *Stephenson*, J. **1932**, 1675).

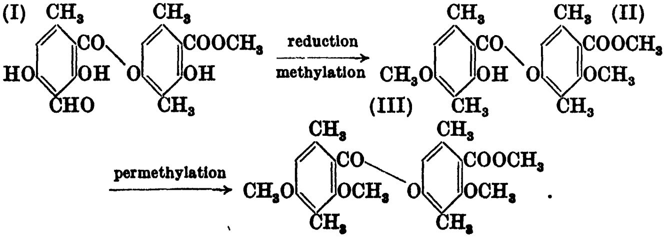
Diffractic acid, *dirhizoninic acid* $C_{20}H_{22}O_7$, m.p. 190° (decomp.) (methyl ester m.p. 127°; methyl ether methyl ester m.p. 106°), was first isolated from the lichen *Usnea longissima* (*Hesse*, J. pr. **73**, 120), and later from *Usnea diffracta* (*Asahina* and *Fuzikawa*, Ber. **65**, 175). It contains two methoxyl groups, and on boiling with alkali decomposes smoothly into the monomethyl ether of rhizoninic acid, methyl-orcinol and CO_2:



This proves the above formula (II). It has been synthesised from the dimethyl ether of methyl-orcinol-carboxylic acid chloride (methyl ether of rhizoninic acid chloride) and the methyl ester of methyl-orcinol-carboxylic acid (atraric acid) (*Asahina* and *Fuzikawa*, Ber. **65**, 583). For the identity of diffractic acid with dirhizoninic acid, see idem, Ber. **65**, 1668.

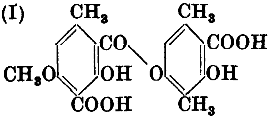
Atranorin, $C_{19}H_{18}O_8$, a paleyellow compound m.p. 196° (trimethyl ether m.p. 123°), is a widely distributed lichen depside, first isolated from *Lecanora atra*; it is decomposed by alkali into atranol $C_8H_8O_3$, m.p. 125° (γ-orcyl-aldehyde, see *Pfau*, Helv. **9**, 650; *Robertson* and *Robinson*, J. **1927**, 2196), CO_2 (from atranol-carboxylic acid) and atraric acid $C_{10}H_{12}O_4$, m.p. 143° (methyl ester of methyl-orcinol-carboxylic acid, p. 381); methyl alcohol yields atranolic methyl ester $C_{10}H_{10}O_5$, m.p. 147° (haematommic methyl ester; synthesis: *Curd*, *Robertson* and *Stephenson*, J. **1933**, 130; *Pfau*, Helv. **16**, 282) and atraric acid. The very mild action of alkali gives atranorinic acid $C_{18}H_{16}O_8$, m.p. 157°, the acid corresponding to atranorin (*Pfau*, Helv. **9**, 650; **11**, 864; *Curd*, *Robertson* and *Stephenson*, loc. cit.).

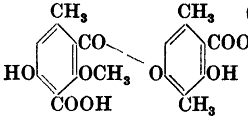
On the basis of these reactions, atranorin is given the following constitution (I); this is further supported by the catalytic reduction of atranorin with Pd-charcoal to nor-barbatinic methyl ester, m.p. 134°, and methylation of the latter to the methyl ether of barbatinic methyl ester (II), m.p. 123°, and to the methyl ether of diffractic methyl ester (III), m.p. 106° (*Asahina* and *Tukamoto*, Ber. **66**, 897):



Squamatic acid (I), $C_{19}H_{18}O_9$, m.p. 215°, can be obtained from the lichen *Cladonia uncialia*; that its constitution can be represented by (I) is shown by its hydrolysis to methyl-orcinol, m.p. 163°, CO_2 (formula p. 381) and the monomethyl ether of orcinol-dicarboxylic acid (formula p. 381), m.p. 208°, or more clearly by the fission of its dimethyl ether dimethyl ester, m.p. 134°, into isorhizoninic methyl ester $C_{11}H_{14}O_4$, m.p. 146°, and the dimethyl ether of orcinol-dicarboxylic acid $C_{11}H_{12}O_4$, m.p. 212° (*Asahina* and *Yanagita*, Ber. **66**, 36):

(I)

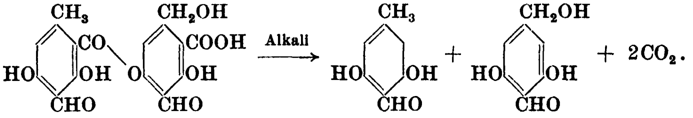




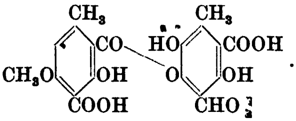
(II)

Iso-squamatic acid (II), $C_{19}H_{18}O_9$, m.p. 227°, occurs in *Cladonia Boryi*. Its hydrolysis leads to the monomethyl ether of orcinol-dicarboxylic acid, m.p. 203°, isomeric with that from squamatic acid, methyl-orcinol and CO_2, and methylation gives a dimethyl ether-dimethyl ester, m.p. 134°, identical with that from squamatic acid (idem, ibid. 393).

Barbatolic acid, $C_{18}H_{14}O_{10}$, m.p. 207° (decomp.), which accompanies barbatinic acid and usnic acid in *Usnea barbata*, can be shown to be the depside of atranol-carboxylic acid (formula p. 381) and barbatol-carboxylic acid (formula p. 381). Fission with alkali yields the corresponding phenolic aldehydes, atranol $C_8H_8O_3$, m.p. 125°, and barbatol $C_8H_8O_4$, m.p. 189°, and 2 mol CO_2 (*Schopf*, *Heuck* and *Duntze*, Ann. **491**, 220), according to the equation:

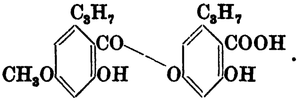


Thamnolic acid, $C_{19}H_{16}O_{11}$, yellowish-white prisms, m.p. 213°, was first found in *Thamnolia vermicularis*, and later in various species of *Cladonia*. Alkaline hydrolysis converts it into the monomethyl ether of orcinol-dicarboxylic acid (formula p. 381) $C_{10}H_{10}O_6$, m.p. 206°, and the decomposition products of thamnol-carboxylic acid (formula p. 381), thamnol $C_8H_8O_4$, m.p. 185°, and CO_2. Fission of the permethylated compound yields the dimethyl ethers of orcinol-dicarboxylic acid and of orcinol (*Pfau*, Helv. **9**, 658; *Asahina* and *Ihara*, Ber. **62**, 1196; **65**, 55; *Asahina* and *Fuzikawa*, ibid. 58). By analogy, it is assumed that the carboxyl para to the methoxyl group in the methyl ether of orcinol-dicarboxylic acid is linked with the phenolic hydroxyl group para to the carboxyl group in thamnol-carboxylic acid, and thus the formula attributed to thamnolic acid is:



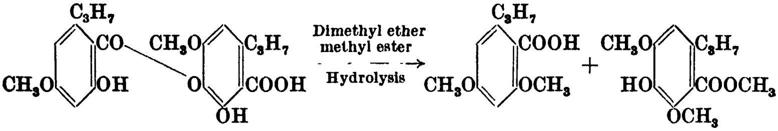
Divaricatic acid $C_{21}H_{24}O_7$, m.p. 137°, can be isolated from the lichen *Evernia divaricata*; it is hydrolysed to divaric acid (formula p. 381), $C_{10}H_{12}O_4$, m.p. 179° (synthesis, *Sonn*, Ber. **64**, 1851; *Asahina* and *Akagi*, Ber. **68**, 1130) and its 4-methyl ether, divaricatinic acid $C_{11}H_{14}O_4$, m.p. 149°; both acids are degraded by HI to divarin $C_9H_{12}O_2$, m.p. 44° (*Hesse*, J. pr. **88**, 24; *Mauthner*, ibid. **108**, 275). The constitution of the fission products has been established by synthesis (*Sonn* and *Scheffler*, Ber. **57**, 959; *Sonn*, Ber. **61**, 2579; **64**, 1851; *Mauthner*, J. pr. **107**, 103). Since hydrolysis of the dimethyl ether of divaricatic methyl ester, m.p. 85°, yields the methyl ether of divaricatinic acid $C_{12}H_{16}O_4$, m.p. 64°, and the methyl ester of iso-divaricatinic acid (2-methyl ether of divaric acid $C_{11}H_{14}O_4$, m.p. 93°), $C_{12}H_{16}O_4$, m.p. 121°

(*Asahina* and *Hirakata*, Ber. **65**, 1665), the lichen acid has the following formula:



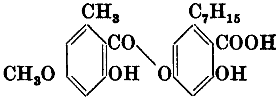
Sekikic acid (I), $C_{22}H_{26}O_8$, m.p. 144° (*diacetate* m.p. 163°: *methyl ester* m.p. 124°), is found with usnic acid and obtusatic acid in the Manchurian drug "shi-hoa", the Japanese "seki-ka", obtained from the lichens of the genus *Ramalina*. When hydrolysed, it gives divaricatinic acid (4-methyl ether of divaric acid) $C_{11}H_{14}O_4$, and 3-hydroxy-divaricatinic acid $C_{11}H_{14}O_5$, m.p. 158°. How the components are esterified is shown by the hydrolysis of the dimethyl ether methyl ester $C_{25}H_{32}O_8$, m.p. 81°, into the methyl ether of divaricatinic acid (II), m.p. 64°, and the methyl ether of 3-hydroxy-divaricatinic methyl ester (III), m.p. 88°:

(I) (II) (III)



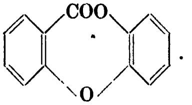
The constitution of the latter acid (III) was proved by its conversion into 3:5-dimethoxy-4-acetoxy-isopropyl-benzene, m.p. 88° (*Asahina* and *Nonomura*, Ber. **66**, 30). For the synthesis of the dimethyl ether of sekikic methyl ester, see *Asahina* and *Yasue*, Ber. **68**, 132; of sekikic acid itself, see idem, ibid. 1133.

The occurrence of the lichen depside **sphaerophorin,** $C_{23}H_{28}O_7$, m.p. 140° (*diacetate* m.p. 134°), has been observed in various species of *Sphaerophorus*. Its constitution



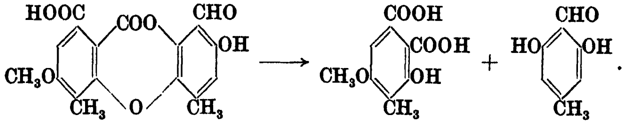
was determined by alkaline hydrolysis to everninic acid (4-methyl ether of orsellinic acid, see p. 381), m.p. 170° (decomp.), sphaerophorol (1-n-heptyl-3:5-dihydroxy-benzene, see p. 381), $C_{10}H_{12}O_4$, m.p. 58°, and CO_2 (*Asahina* and *Hashimoto*, Ber. **67**, 416).

Certain depsides are placed in a special group; these are diphenyl ethers as well as depsides, and contain one hydroxy-hydroquinone nucleus; e.g. psoromic acid, salazinic acid, stictic acid and cetraric acid. Their structures are derived from the following ring-system:



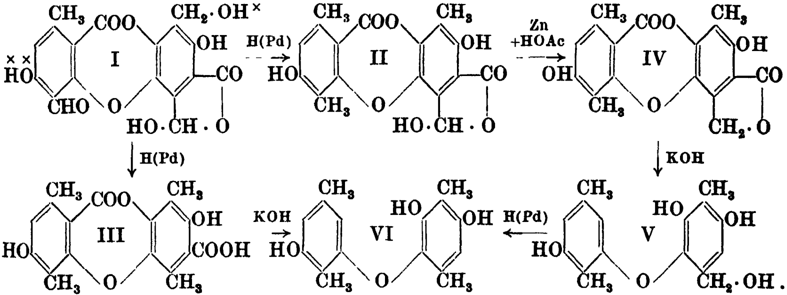
These diphenyl ether depsides are called by Asahina the "depsidones" (*Asahina*, Acta phytochim. 8 (1934), 33, 47); one of their characteristic properties is to give a colouration with amines, such as aniline, and in particular with benzidine, p-phenylene diamine and KOH. This reaction makes it easy to show the presence of these acids in the thallus of lichens (loc. cit.).

Psoromic acid, *parellic acid*, $C_{18}H_{14}O_8$, m.p. 264° (decomp.), can be obtained from the lichen *Psoroma crassum* and is characterised by its mono-anil, decomp. 299°, and a triacetate, m.p. 179°. The depside link is broken even by cold potash, giving *parinic acid* $C_{18}H_{16}O_9$, m.p. 235° (decomp.). The products obtained by dry distillation provide evidence for the structure of the acid, because it decomposes uniquely into 3-hydroxy-5-methoxy-4-methyl-phthalic acid $C_{10}H_8O_5$, m.p. 266°, monomethyl ether m.p. 166°), and atranol, $C_8H_8O_3$, m.p. 125° (*Asahina* and *Hayashi*, Ber. **66**, 1023):



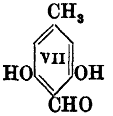
The structure of **salazinic acid** (I), $C_{18}H_{12}O_{10}$, decomp. 240–260° (triacetate m.p. 207°; hexacetate m.p. 178°; diphenylhydrazone m.p. 270–295°), from *Parmelia conspersa, cetrata* and *saxtilis*, etc. (*Hesse*, J. pr. **62**, 474; **63**, 536; *Asahina* and *Tanase*, ibid. **67**, 1434; *Zopf*, Ann. **352**, 6; *Asahina*, J. Pharm. Soc. Japan **1926**, no. 533, 47) has been determined by a combination of hydrogenation and alkali degradation (*Asahina* and *Asano*, Ber. **66**, 689, 893, 1031, 1215).

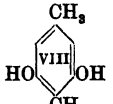
Catalytic hydrogenation (with Pd-charcoal) gives at first hyposalazinic acid $C_{18}H_{14}O_8$ (II), decomp. 240–280° (trimethyl ether m.p. 165°), and hypoproto-cetraric acid (see p. 388) $C_{18}H_{16}O_7$ (III), decomp. 215–242° (dimethyl ether methyl ester m.p. 170°); further reduction of (II) with Zn and acetic acid gives hyposalazinolide $C_{18}H_{14}O_7$ (IV), m.p. 300° (dimethyl ether m.p. 283°). The latter reduction product can be decarboxylated with 50% KOH to hyposalazinol $C_{16}H_{18}O_5$ (V), m.p. 197° (trimethyl ether m.p. 146°) which by hydrogenation gives desoxy-hyposalazinol $C_{16}H_{18}O_4$ (VI), m.p. 185° (trimethyl ether m.p. 95°), identical with the decarboxylation product of (III):

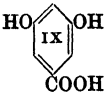


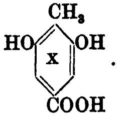
$^{\times}OCH_3$ instead of OH = α-Methyl ether of salazinic acid (p. 388)
$^{\times\times}OCH_3$ instead of OH = β-Methyl ether of salazinic acid (p. 388)

The determination of the constitution of the above compounds is carried out by pyrogenic degradation and fusion with potash. While the dry distillation of salazinic acid itself leads to atranol (VII, below) $C_8H_8O_3$, m.p. 125°, the reduction products yield methyl-orcinol (VIII) $C_8H_{10}O_2$, m.p. 163°, showing that the aldehyde group has been reduced to a methyl group. Potash fusion eliminates the hydroxy-methyl group from the second half of the molecule of salazinic acid, giving α-resorcylic acid (IX) $C_7H_6O_4$, m.p. 232°, while the hydro-derivative gives the second half as 3:5-dihydroxy-p-toluic acid (X) $C_8H_8O_4$, m.p. 262° (dimethyl ether methyl ester m.p. 105°):





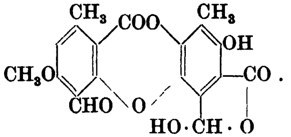




These results lead to formula (I) for salazinic acid.

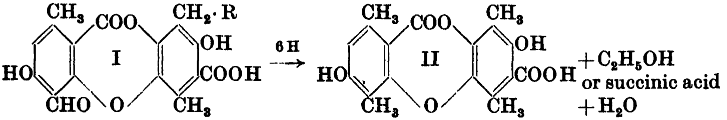
The lichen *Usnea articulata* var. *asperula* Müll. Arg. contains two acids $C_{19}H_{14}O_{10}$, m.ps. 210° (decomp.) and 252° (decomp.), which have been shown from their fission products to be α- and β-methyl ethers of salazinic acid (formulae, p. 387) respectively (*Asahina* and *Tukamoto*, Ber. **67**, 963).

Stictic acid, $C_{19}H_{14}O_9$, m.p. 269° (diacetate m.p. 236°; tetracetate m.p. 222°; dianil dec. 165°), from the lung lichen *Sticta pulmonaria* (*Hesse*, J. pr. **57**, 441; **70**, 491) and from *Ramalina scopulorum* (*Hurd* and *Robertson*, J. **1935**, 1379), can be reduced to the monomethyl ether of hyposalazinic acid (see p. 387), $C_{19}H_{16}O_8$, m.p. 264°, and of hyposalazinolide $C_{19}H_{16}O_7$ (p. 387); thermal degradation gives atranol monomethyl ether $C_8H_7O_2(OCH_3)$, m.p. 78°. This identifies it as the monomethyl ether of desoxy-salazinic acid (*Asahina*, *Yanagita* and *Omaki*, Ber. **66**, 943; *Asahina*, *Yanagita*, *Hirakata* and *Ida*, ibid. 1080; *Asahina* and *Asano*, ibid. 1215; *Asahina* and *Yanagita*, ibid. **67**, 1965):



The demethylation product, **nor-stictic acid** $C_{18}H_{12}O_9$, m.p. 283° (decomp.) (pentacetate m.p. 212°; dianil m.p. 265°) is also found in these lung lichens (idem, ibid. **67**, 799).

Cetraric acid (I, R = R$_1$), $C_{20}H_{18}O_9$ (dimethyl ether methyl ester m.p. 152°; anil m.p. 250°), is present in Iceland moss, *Cetraria islandica*, as fumaro-proto-cetraric acid (I, R = R$_2$), decomp. 240–260° (*Koller* and *Kandler*, Mo. **56**, 234), and is obtained from the lichen as the acid because of alcoholysis. Catalytic reduction of either acid with Pd converts a formyl group into a methyl group, and, in addition, the former loses its ethoxy-group and the latter its fumaric acid residue, with the formation in both cases of hypo-proto-cetraric acid $C_{18}H_{16}O_7$ (II), decomp. 215–245° (dimethyl ether methyl ester m.p. 170°); the latter compound is also obtained as a by-product from salazinic acid under the same conditions (see p. 387). The carbon skeleton of the acid is thus essentially proved, but the position of the alcoholic hydroxyl remained to be settled. This was established by the potash fusion of cetraric acid and its reduction product: the half of the molecule of cetraric acid which was uncertain was degraded to α-resorcylic acid (3:5-dimethoxy-benzoic acid, m.p. 182°), while the hydro-product gave 3:5-dihydroxy-p-toluic acid (3:5-dimethoxy-p-toluic methyl ester, m.p. 105°). The following formulae therefore show the hydrogenation of this lichen acid (*Asahina* and *Tanase*, Ber. **66**, 700; *Asahina* and *Asano*, ibid. 893; 1215; *Asahina* and *Tanase*, Ber. **67**, 411):



R$_1$ = OC$_2$H$_5$ Cetraric acid
R$_2$ = OOC·CH:CH·COOH Fumaro-proto-cetraric acid.

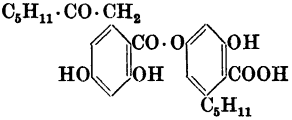
Capraric acid, $C_{18}H_{14}O_9$, decomp. 220–250° (mono-acetate decomp. 220–250°), which occurs in the Japanese lichen *Parmelia caperata*, has been shown to be the parent hydroxy-compound of cetraric acid (proto-cetraric acid (I), R = OH) (*Asahina* and *Yanagita*, Ber. **66**, 1217; *Asahina* and *Tanase*, Ber. **67**, 766).

The following group of lichen acids are distinguished by the fact that their molecules contain one ketonic group, as in olivetoric acid and physodic acid, or several such groups, as in alectoronic acid and collatolic acid, in a residue attached to an aromatic nucleus, e.g. $-CH_2\cdot CO\cdot C_5H_{11}$. Some of them also have a diphenyl ether structure, and thus belong to the depsidones (see p. 386). The formation of keto-enol-lactones as fission products is also characteristic of these compounds, e.g. olivetonide or the mono-methyl ether of olivetonide.

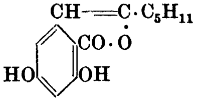
Olivetoric acid, $C_{26}H_{32}O_8$, m.p. 151°, has been found in *Parmelia olivetorina* and in the Japanese lichen *Alectoria divergens* (*Zopf,* Ann. **313,** 342; *Hesse,* J. pr. **94,** 227). Fission of the acid with formic acid or methyl alcohol leads to olivetol $C_{11}H_{16}O_2$, and CO_2, which are the decomposition products of olivetol-carboxylic acid $C_{12}H_{16}O_4$ (formula p. 381), and olivetonide $C_{14}H_{16}O_4$ (dimethyl ether m.p. 94°). The side-chain C_5H_{11} of the dihydroxy-benzene $C_{11}H_{16}O_2$ was shown to be normal by its oxidation to n-caproic acid. Olivetonide is hydrolysed by hot caustic potash to olivetonic acid

$$HOOC\cdot C_6H_2(OH)_2\cdot CH_2\cdot CO\cdot C_5H_{11}$$

(formula p. 381); its dimethyl ether is oxidised by permanganate to 3:5-dimethoxy-o-phthalic acid and n-caproic acid; hence its structure is 3-n-amyl-6:8-dihydroxy-isocoumarin. When diazomethane is allowed to react with olivetoric acid for a short time, the product is a dimethyl ether methyl ester, which is converted by alcoholic potash into the 2-monomethyl ether of olivetol-carboxylic acid methyl ester and the monomethyl ether of olivetonide (3-n-amyl-6-methoxy-8-hydroxy-isocoumarin), $C_{15}H_{18}O_4$, m.p. 57° (*Asahina* and *Asano,* Ber. **65,** 475, 584).

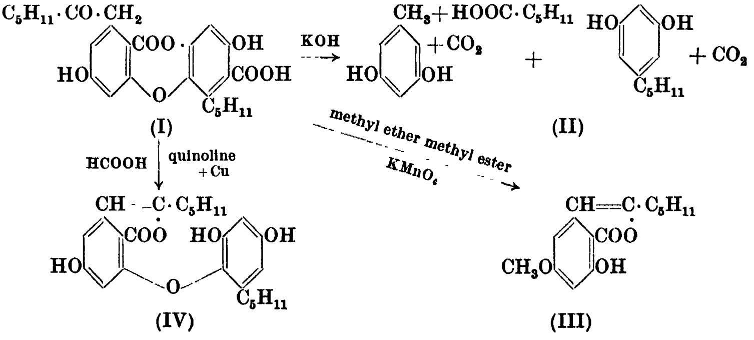


Olivetoric acid



Olivetonide.

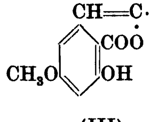
The same components (olivetol-carboxylic acid and olivetonic acid formulae p. 381) are present in **physodic acid** (I), $C_{26}H_{30}O_8$, m.p. 205° (monoxime m.p. 210°; diacetate m.p. 155°), obtained from the Japanese lichen *Parmelia physodes.* This is shown by the products obtained by potash fusion (II), which are orcinol, n-caproic acid, CO_2 (from VIII), olivetol (n-amyl-resorcinol) and CO_2 (from VII). The monomethyl ether of physodic methyl ester, m.p. 119°, is oxidised by $KMnO_4$ to the monomethyl ether of olivetonide (III). By treatment of the lichen acid with formic acid or with quinoline and Cu it undergoes enol-lactonisation and simultaneous decarboxylation, yielding physodone $C_{25}H_{30}O_6$ (IV), m.p. 199°. The following scheme shows the essential reactions upon which the constitution is based (*Asahina* and *Nogami,* Ber. **67,** 805):



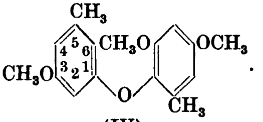
Alkali degradation of the trimethyl ether of physodic dimethyl ester leads to proto-physodon $C_{21}H_{28}O_4$, caproic acid and two mol. of CO_2; bromination and CrO_3-oxidation of this diphenyl-ether gives the corresponding quinones (*Asahina* and *Nogami*, Ber. **68**, 77). For the synthesis of a derivative of physodic acid, see idem, ibid. **68**, 1500.

The following two acids are closely related to physodic acid: **alectoronic acid,** $C_{28}H_{32}O_9$, m.p. 193° (triacetate m.p. 123°; trimethyl ether methyl ester m.p. 114°; dioxime m.p. 194°), obtained from species of the Japanese *Alectoria* (*Asahina* and *Hashimoto*, Ber. **66**, 641), and its monomethyl ether, **collatolic acid** (I), $C_{29}H_{34}O_9$, m.p. 125°, from *Cetraria collata* (*Asahina, Kanaoka* and *Fuzikawa*, ibid. 649).

The acids are lactonised by boiling with formic acid, to give alectorone $C_{28}H_{30}O_8$, m.p. 198° (triacetate m.p. 158°; monoxime m.p. 226°) and collatolone (II), $C_{29}H_{32}O_8$, m.p. 142°. The products obtained from the potash fusion of alectoronic acid, viz. two mol. of caproic acid (anilide m.p. 98°), orcinol, m.p. 58°, 5-hydroxy-1:3-dimethyl-benzene $C_8H_{10}O$, m.p. 60°, and the corresponding 5-hydroxy-1-methyl-benzene-3-carboxylic acid $C_8H_8O_3$, m.p. 208°, indicate that the molecule contains two different aromatic nuclei. Oxidation of the monomethyl ether with permanganate gives the monomethyl ether of olivetonide (III), which is already known (for the proof of its constitution, see p. 389):

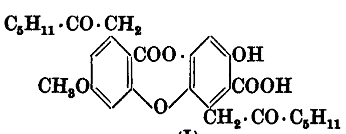


(III)

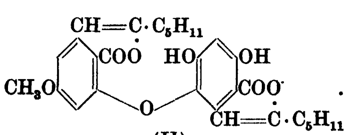


(IV)

Important conclusions can be drawn from the formation of the dimethylether derivative, the trimethyl ether of alectol $C_{17}H_{20}O_4$ (IV), m.p. 96°, from the dimethyl ether of collatolic methyl ester by treatment with alcoholic potash followed by formic acid. The constitution of this compound has been determined by degradation to orcinol, m.p. 58°, and α-resorcylic acid (3:5-dihydroxy-benzoic acid), m.p. 232°, or to two mol. of methoxytoluquinone, m.p. 151°, and by its synthesis from the potassium salt of orcinol monomethyl ether and bromo-orcinol dimethyl ether. The ready formation of the methyl ether of olivetonide (III) shows that in the natural product there is a caproyl residue on the 5-methyl group and a carboxyl group on the 6-carbon atom of alectol. The occurrence of a di-enol-lactone (collatone [II]) leads to the assumption that the second aromatic residue has a similar structure. Since it gives a positive chloride of lime reaction (showing the presence of two meta-hydroxyl groups), the formula (I) is given to collatolic acid (*Asahina* and *Fuzikawa*, Ber. **67**, 163):



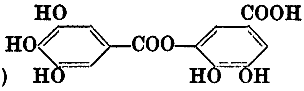
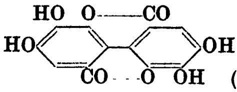
(I)

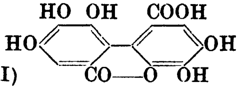


(II)

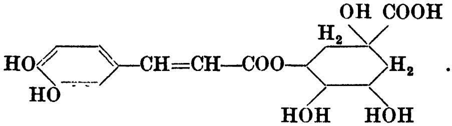
The depsides so far considered have been almost entirely derivatives of resorcinol, but tannin-like substances are known which contain a gallic acid nucleus.

m-Digallic acid (I), **ellagic acid** (II) and **luteolic acid** (III), condensation products of gallic acid, play an important part as constituents of sugaresters (see p. 392).

(I)   (II)

(III) 

The tannin of coffee beans, **chlorogenic acid** $C_{16}H_{18}O_9$, was discovered by *Payen* in 1849 (Ann. Chim. Phys. **26**, 108) and is present in the beans as the potassium caffeine salt $C_{16}H_{17}O_9K \cdot C_8H_{10}O_2N_4$, to the extent of about 3–4%. Dilute sulphuric acid sets free the acid, which is hydrolysed by moulds or by tannase (*Freudenberg*, Ber. **53**, 232) to 3 : 4-dihydroxy-cinnamic acid and quinic acid (1:3:4:5-tetrahydroxy-cyclohexane-1-carboxylic acid, α-hydroxy-hexahydro-gallic acid [p. 135], see *Fischer* and *Dangschat*, Ber. **65**, 1109). The formation of a complex of chlorogenic acid and acetone, which is insoluble in bicarbonate, and the fission of its permethylation product to 3:4-dimethoxy-cinnamic acid and the 1:4:5-trimethyl ether of quinic acid, which can form a lactone (idem, ibid. 1037), shows that the acid has the structural formula:

 .

The following anthocyanin-depsides fall under the Natural Colouring Matters (see pp. 449 and 450):

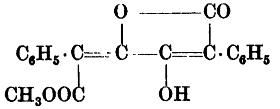
Salvianin, $C_{30}H_{32}O_{18}$, the malonic acid depside of pelargonidin-diglucoside, from *Salvia coccinea* (*Willstatter* and *Bolton*, Ann. **412**, 113).

Delphinin, $C_{41}H_{38}O_{21}$, the p-hydroxy-benzoic acid depside of delphinidin-diglucoside, from the larkspur, *Delphinium consolida* (*Willstatter* and *Mieg*, Ann. **408**, 61; *Karrer* and *Widmer*, Helv. **10**, 5, 67; *Karrer* and *Schwarz*, Helv. **11**, 916).

Monardaein, $C_{36}H_{36}O_{17}$, the p-hydroxy-cinnamic acid depside of pelargonidin diglucoside, from the sweet bergamot, *Monarda didyma* (*Karrer* and *Widmer*, Helv. **10**, 67; **11**, 837).

Gentianin, $C_{30}H_{26}O_{14}$, the p-hydroxy-cinnamic acid depside of the delphinidin-glucoside from *Gentiana* (idem, ibid. **10**, 73).

Finally, among the depsides mention may be made of a closely related type of compound with an enol-ester structure, **vulpinic acid,** $C_{18}H_{14}O_5$,



which occurs in lichens, and its p-methoxy-derivative, pinastrinic acid (for their constitution, see under natural colouring matters, p. 438).

A great number of depsides still uninvestigated will be found in the list given in the monograph on Lichen Substances, by *W. Brieger*, in *Abderhalden's* Handbuch der biolog. Arbeitsmethoden, Lfg. 20.

(β) SUGAR-ESTERS

The mono-acyl derivatives of the sugars, the simplest members of this class of compounds, do not show the typical protein precipitation reaction of the true tannins; this depends on the presence of phenol-carboxylic acid residues in the tannin molecule.

Luteic acid, which can be built up from glucose by *Penicillium luteum* (*Raistrick* and *Rintoul,* Phil. Trans. B. **220** [1931], 1), is an acyl derivative of a complex carbohydrate, lutcose. Complete hydrolysis with dilute H_2SO_4 gives two mol. glucose and one mol. *malonic acid.*

Vaccinin, $C_{13}H_{16}O_7$, $[\alpha]_D$ + 48°, has been isolated from the juice of the whortleberry (*Vaccinium vitis idaea*). The compound has reducing properties and forms a phenylhydrazone, but no osazone; it is probably 2-benzoyl-glucose (*Ohle,* Biochem. Z. **131**, 611).

Dibenzoyl-glucoxylose, $C_{25}H_{28}O_{12}$, m.p. 148°, $[\alpha]_D$ — 106·7°, is found in the twigs of *Daviesia latifolia* (*Power* and *Salway,* J. **105**, 767, 1062; *Tutin,* J. **107**, 7).

Salireposide, $C_{20}H_{22}O_{10}$, m.p. 157° and 206°, $[\alpha]_D$ — 36·8, which occurs in various species of *Salix,* gives on hydrolysis benzoic acid, glucose and a compound $C_7H_6O_3$ (*Rabaté,* Bull. Soc. Chim. biol. **17** (1935), 328).

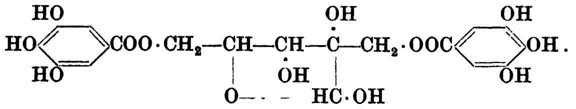
Orobanchin, from the bulbs of *Orobanche rapum,* can be hydrolysed to caffeic acid, glucose and rhamnose (*Bridel* and *Charaux,* C. r. **178**, 1839).

Glucogallin, $C_{13}H_{16}O_{10}$, m.p. 212° (decomp.), $[\alpha]_D$ — 25 (H_2O), *heptacetate* m.p. 126°, $[\alpha]_D$ — 24·4°, from the roots of the rhubarb, *Rheum officinale* (*Gilson,* C. 1903 I, 882), has been identified as *l*-galloyl-β-glucose by its synthesis from 2:3:4:6-tetracetyl-glucose and triacetyl-galloyl chloride (*Feist,* Ber. **45**, 1493; *Fischer* and *Bergmann,* Ber. **51**, 298, 1760, 1791).

Acertannin, $C_{20}H_{20}O_{13}$, m.p. 165°, $[\alpha]_D$ + 20·5° (acetone), acetate m.p. 155°, is found in a maple, *Acer ginuola,* indigenous to Korea. Hydrolysis with 5% H_2SO_4 gives two mol. gallic acid and an unknown sugar, "aceritol" $C_6H_{12}O_5$ (tetracetyl-compound m.p. 75°), see *Perkin* and *Uyeda,* J. **121**, 66.

Tetrarin, $C_{32}H_{32}O_{12}$, m.p. 205°, which is also contained in rhubarb, is decomposed by hydrolysis into glucose, cinnamic acid, $C_9H_8O_2$, gallic acid, $C_7H_6O_5$, and "rheosmin", $C_{10}H_{12}O_2$, m.p. 79·5° (probably hydroxy-cumin-aldehyde) (see *Gilson,* C. r. **136**, 385; C. 1903 I 882; *Feist,* Chem. Ztg. **32**, 918).

Hamamelitannin, $C_{20}H_{20}O_{14}$, m.p. 117°, is found in the witch hazel, *Hamamelis virginiana.* Hydrolysis with tannase gives two mol. gallic acid and hamamelose, $[\alpha_D]$ — 15°, a hexose with a branched chain, as is shown by the reduction of the corresponding hexonic acid to methyl-propyl-acetic acid (*Schmidt,* Ann. **476**, 250). The tannin can be allotted the following formula (*Freudenberg,* Ber. **52**, 177; *Freudenberg* and *Peters,* Ber. **53**, 953; *Freudenberg* and *Blümmel,* Ann. **440**, 45):



The East Indian myrobalans, the fruits of *Terminalia chebula,* contain 3—4% of **chebulic acid,** $C_{41}H_{34}O_{27}$, $[\alpha]_D$ + 15° ($CH_3OH + H_2O$), which is hydrolysed by dilute NaOH or by tannase according to the equation (*Freudenberg,* Ber. **52**, 1238; *Freudenberg* and *Fick,* Ber. **53**, 1728):

$$C_{41}H_{34}O_{27} + 5H_2O \rightarrow \underset{\text{dibas. hydroxy-acid}}{C_{14}H_{14}O_{11}} + \underset{\text{gallic acid}}{3C_7H_6O_5} + C_6H_{12}O_6$$

The unknown hydroxy-acid shown in this equation is combined with glucose through a hydroxyl group and through one carboxyl group; the second carboxyl is free; of the three gallic acid residues, two at least are attached directly to the sugar molecule. In agreement with this, partial hydrolysis yields digalloyl-glucose, gallic acid and the unknown hydroxy-acid (*Freudenberg* and *Frank,* Ann. **452**, 303).

Turkish tannin, $[\alpha]_D$ + 95°, from *Quercus infectoria* (Aleppo galls), is hydrolysed to five mol. gallic acid and one mol. glucose (*Fischer* and *Freudenberg,* Ber. **47**, 2485). Synthetic pentagalloyl-glucose shows a very striking similarity to the natural product (*Fischer* and *Bergmann,* Ber. **51**, 1779; **52**, 836).

Sumach-tannin, obtained in Mediterranean countries from *Rhus coriaria,* etc., also contains pentagalloyl-glucose together with ellagic acid (*Löwe,*

Z. anal. Chem. **12**, 128; *Stenhouse*, Ann. **45**, 11; J. **11**, 401; *Strauss* and *Geschwendner*, Z. angew. Chem. **19**, 1124).

Chinese tannin, $[\alpha]_D + 76°$, is obtained from *Rhus semialata*, and contains 10 mol. of gallic acid to 1 mol. of glucose. The permethylated compound, methylotannin, obtained by the use of diazomethane, is hydrolysed by alkali into 5 mol. of the trimethyl ether of gallic acid, 5 mol. of the 3:4-dimethyl ether of gallic acid, and 1 mol. of glucose; hence the compound is penta-m-digalloyl-glucose (*Herzig* and *Tscherne*, Ber. **38**, 989; *Herzig* and *Renner*, Mo. **30**, 543). The synthetic tannin corresponds very closely to the natural product (*Fischer* and *Freudenberg*, Ber. **46**, 1127; *Fischer*, Ber. **52**, 826; *Freudenberg* and *Scilasi*, Ber. **55**, 2813; **56**, 406).

The ellagic acid group of tannins is also widely distributed. **Ellagic acid,** $C_{14}H_6O_8$ (see p. 390) (tetracetyl-compound m.p. 346°) has been found e.g. with gallic acid and sugar in divi-divi pods of species of *Caesalpinia*, in carob beans (*Alpers*, Arch. Pharm. **244**, 515), in the pomegranate tree (*Punica granatum*) (*Rembold*, Ann. **148**, 285), etc.

Ellagic acid dimethyl ether, $C_{16}H_{10}O_8$, m.p. 338° (diacetate m.p. 300°), occurs in *Euphorbia formosa* (*Shinoda* and *Kun*, J. Pharm. Soc. Japan **51** (1931), 50).

The myrobalans appear to contain a diglucose ester of luteolic acid (p. 398), **ellagen-tannic acid,** $C_{26}H_{28}O_{18}$ (*Nierenstein*, Ber. **48**, 1267).

Gall tannin is contained in the galls produced by *Cynips calicis* on unripe acorns of *Quercus cerris*. Complete hydrolysis gives glucose and ellagic acid. Since, however, hydrolysis of the permethylated tannin, followed by methylation, yields the pentamethyl ether of luteolic methyl ester, m.p. 111°, the natural product must be a luteolic acid glucoside (*Nierenstein*, J. **115**, 1174).

Ellagic acid, gallic acid, quercetin and glucose can be isolated from the wood of the chestnut (*Castanea vesca*) (*Freudenberg* and *Walpuski*, Ber. **54**, 1695).

The **tannin of the oak** (*Quercus pedunculata*, etc.) is based, according to Freudenberg, upon a new tannin acid, *quercussic acid* (*Freudenberg* and *Vollbrecht*, Ann. **429**, 284), which contains glucose as a glucoside and ellagic acid as an ester; the fission products are obtained by fermentative degradation (idem, Ber. **55**, 2420; *Nierenstein*, J. **115**, 1174).

(b) CONDENSED TANNINS AND RESIN ACIDS

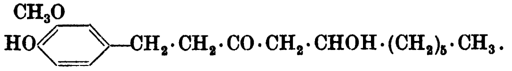
These can be grouped into derivatives of pyrocatechol and those of phloroglucinol.

The simplest members of this class of compounds are p-hydroxy-acetophenone and acetovanillone, which occur naturally as the glucosides **picein** (p. 356) and **androsin** (p. 356).

Gingerone (*Zingerone*), $C_{11}H_{14}O_3$, m.p. 41°, is isolated from the ginger, *Zingiber officinale*, together with gingerol and shogaol. Its mono-methyl ether is oxidised by permanganate to veratric acid, $(CH_3O)_2C_6H_3 \cdot COOH$, and is degraded by hypobromite to β-3:4-dimethoxyphenyl-propionic acid, $(CH_3O)_2C_6H_3 \cdot CH_2 \cdot CH_2 \cdot COOH$, and thus must be 3:4-dimethoxy-benzyl-acetone, $(CH\ O)_2C_6H_3 \cdot CH_2 \cdot CH_2 \cdot COCH_3$, m.p. 56° (oxime m.p. 93°). The constitution of gingerone as 3-methoxy-4-hydroxy-benzyl-acetone has been proved by its synthesis from vanillin and acetone via 3-methoxy-4-hydroxy-styrylmethyl ketone, m.p. 129° (*Nomura*, J. **111**, 769).

Shogaol, $C_{17}H_{22}O_3$, a yellow oil of b.p. 231—238°/15 mm., which occurs with gingerone in ginger, is an $\alpha\beta$-unsaturated ketone (dihydro-compound $C_{17}H_{24}O_3$, m.p. 31°; benzoy compound m.p. 63°; semicarbazone m.p. 104·5°, see *Nomura* and *Tsurumi*, Sci. Rep. Tohoku **16** [1927], 581). Its formula $(CH_3O)(HO)C_6H_3 \cdot CH_2 \cdot CH_2 \cdot CO \cdot C_7H_{13}$ is based upon similar degradations (*Nomura*, ibid. **7** [1918], 67); its synthesis from gingerone and n-caproic aldehyde shows it to be 3-methoxy-4-hydroxy-phenylethyl-$\Delta^{1:2}$-heptenyl ketone (*Nomura* and *Tsurumi*, Proc. Imp. Acad. Tokyo **2** [1926,] 229; **3**, 159).

Gingerol, $C_{18}H_{28}O_4$, a yellow oil, also prepared from ginger, has been shown to be a ketol of the following constitution by its formation from gingerone and n-heptaldehyde (*Lapworth, Pearson* and *Royle*, J. **111**, 777):



Compounds of similar type to these three substances are contained in the following tannin acids:

"Urushiol", from the Japanese lac from *Rhus vernicifera*, is a mixture of hydro-urushiol, $C_{21}H_{36}O_2$, urushiol $C_{21}H_{34}O_2(1 \models)$ and dehydro-urushiol $C_{21}H_{32}O_2 (2 \models)$. The latter compound is identical with "bhilawanol", the bitter substance of the ink nut, *Senecarpus anacardium* (*Pillay* and *Siddiqui*, J. Indian Chem. Soc. 8 [1931], 517). Oxidation of hydro-urushiol, m.p. 58°, with permanganate gives palmitic acid, while its dimethyl ether, m.p. 37°, yields 3:4-dimethoxy-benzoic acid (*Majima* and *Nakamura*, Ber. **46**, 4080). The position of the double bonds in the side chain of both unsaturated acids can be determined from the products of ozonolysis, which are heptanal or heptanoic acid, and formaldehyde or formic acid together with 3:4-dimethoxyphenyl-n-octanoic acid and azelaic acid. The following formulae must therefore be allotted to the acids from "urushiol" (*Majima*, Ber. **55**, 172):

$$\begin{array}{l}(HO)_2C_6H_3\cdot(CH_2)_{14}\cdot CH_3\\(HO)_2C_6H_3\cdot(CH_2)_7\cdot CH{=}CH\cdot(CH_2)_5\cdot CH_3\\(HO)_2C_6H_3\cdot(CH_2)_7\cdot CH{=}CH\cdot(CH_2)_4\cdot CH{=}CH_2\,.\end{array}$$

The synthesis of the dimethyl ether of hydro-urushiol was carried out from β-(3:4-dimethoxyphenyl)-propionyl chloride and sodium-dodecine, in the following stages (*Majima*, Ber. **48**, 1593; *Majima* and *Tahara*, ibid. 1606):

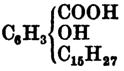
$$\begin{array}{c}(CH_3O)_2C_6H_3\cdot CH_2\cdot CH_2\cdot COCl + NaC{\equiv}C\cdot(CH_2)_9\cdot CH_3\\ \downarrow\\ (CH_3O)_2C_6H_3\cdot CH_2\cdot CH_2\cdot CO{-}C{\equiv}C\cdot(CH_2)_9\cdot CH_3\\ \downarrow \; Pt + H_2\\ (CH_3O)_2C_6H_3\cdot CH_2\cdot CH_2\cdot CO\cdot(CH_2)_{11}\cdot CH_3\\ \text{Clemmensen} \downarrow \text{reduction}\\ (CH_3O)_2\cdot C_6H_3\cdot(CH_2)_{14}\cdot CH_3\,.\end{array}$$

Thitsiol, $C_{23}H_{36}O_2$, an oil from the thitsi- or Burma-lac from *Melanorrhoea usitata*, is catalytically hydrogenated to tetrahydro-thitsiol, $C_{23}H_{40}O_2$, m.p. 96°; this is identical with 1-n-heptadecyl-3:4-dihydroxy-benzene, which has been synthesised by the condensation of margaric acid and pyrocatechol, followed by Clemmensen reduction. Thitsiol is therefore 1-n-heptadecadienyl-3:4-dihydroxy-benzene (*Majima*, Ber. **55**, 191).

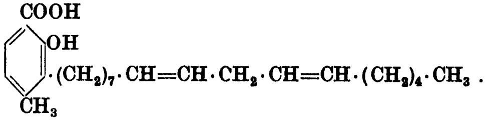
The tsuta-urushi-lac obtained from *Rhus succedanea*, which grows in Indochina and Formosa, contains the closely related **laccol,** $C_{22}H_{34}O_2$, m.p. 23°. Its relationship to thitsiol is shown by the permanganate oxidation of its tetrahydro-derivative (1-n-hexadecyl-2:3-dihydroxy-benzene), m.p. 64° (diacetate m.p. 57.6°), to stearic acid. Ozonolysis of laccol yields nonane-1:9-dicarboxylic acid and formic acid, and hence it is given the constitution: 1-(1:12-hexadecadienyl)-2:3-dihydroxy-benzene (idem, ibid.; *Bertrand* and *Brooks*, C. r. **195**, 405; Bull. Soc. chim. **53** (1933), 432).

The latex of the kambodja lac tree (*Melanorrhoea laccifera*) contains a methyl homologue of the latter, **moreakol,** $C_{23}H_{36}O_2$, m.p. 28°, b.p. 242–250°/0·5 mm., diacetate b.p. 233–240°/0·3 mm. (tetrahydro-compound, b.p. 280–290°/12 mm.; diacetate m.p. 70·5°) (idem, C. r. **197**, 661).

Anacardic acid (I), $C_{22}H_{32}O_3$, m.p. 23–25° (*Pillay*, J. Indian Chem. Soc. **12** [1935], 226), is a phenol-carboxylic acid isolated from *Anacardium occidentale* and *A. orientale*. When its tetrahydro-methyl-ether methyl ester is vigorously oxidised with CrO_3, the aromatic nucleus is destroyed and the product is palmitic acid. Decarboxylation of anacardic acid gives a homologue of phenol, $C_{21}H_{32}O$; this is hydrogenated with platinum oxide and hydrogen to the cyclic alcohol, $C_{21}H_{42}O$, m.p. 31°, the aromatic nucleus being reduced as well as the aliphatic double bonds. This alcohol can be dehydrated and reduced to pentadecyl-cyclohexane, m.p. 25°. Anacardic acid is tentatively given formula I; the positions of the substituents in the benzene nucleus and the positions of the double bonds in the side-chain are still unknown (*Smit*, C. 1931 I 2625):

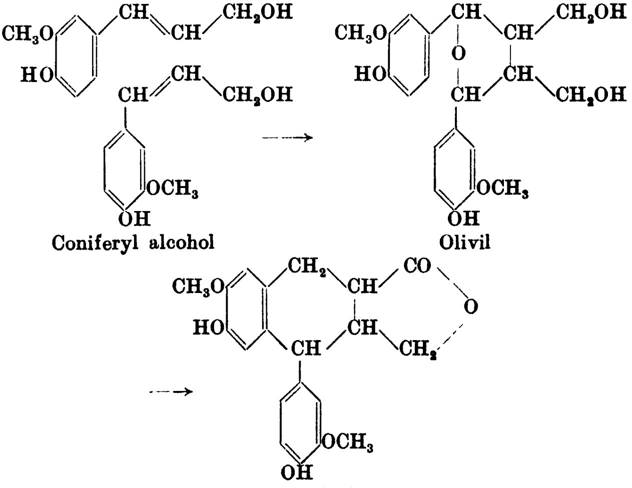
(I) 

$$C_6H_3\begin{cases}COOH\\OH\\C_{15}H_{27}\end{cases}$$

(II) 

Pelandjauic acid (II), $C_{25}H_{38}O_3$, m.p. 26°, is found in the exudations from the wood of *Pentaspadon Motleyi* (Sumatra), and is used in the Dutch Indies for skin diseases. Catalytic hydrogenation of the acid with Pt and H_2 gives a tetrahydro-compound, $C_{25}H_{42}O_3$, m.p. 94°; the methyl ether methyl ester of this, $C_{27}H_{46}O_3$, m.p. 46°, takes up a further 6 atoms of hydrogen with Pt oxide, and is converted into the decahydro-compound, $C_{27}H_{52}O_3$, m.p. 51°. After the saturation of the two double bonds the side chain appears on oxidation with chromic acid as stearic acid. The ozonolysis products of pelandjauic acid, viz. azelaic acid, caproic acid and malonaldehyde (?), show the structure of the unsaturated side-chain (formula II). Pelandjauic acid, like anacardic acid, can be converted into a phenol $C_{24}H_{38}O$, b.p. 210–215°/ 0·5 mm., and into the corresponding cyclohexanol-derivative $C_{24}H_{48}O$, m.p. 35°, and the action of $ZnCl_2$ upon the cyclic alcohol gives a mixture of two unsaturated monocyclic hydrocarbons $C_{24}H_{46}$, formed by dehydration in two directions. Ozonolysis of the hydrocarbon opens the ring, yielding a ketonic acid $C_{24}H_{46}O_3$, m.p. 50°, and a dicarboxylic acid $C_{24}H_{46}O_4$; the phenolic hydroxyl is hence adjacent to the alkyl residue (*van Romburgh* and *van Veen*, C. 1929 II 2784; *van Romburgh* and *Smit*, C. 1930 II 2907). A methyl group must also be present on the benzene nucleus: Zn dust distillation of the phenol $C_{24}H_{38}O$ does in fact give 1-methyl-naphthalene (*idem*, C. 1931 I 96).

Next comes a group of phenolic substances, most of which contain a lactone ring, and occur in natural resins. They are related in structure to eugenol, coniferyl alcohol or ferulic acid, as is shown, for example, in the following formulae:



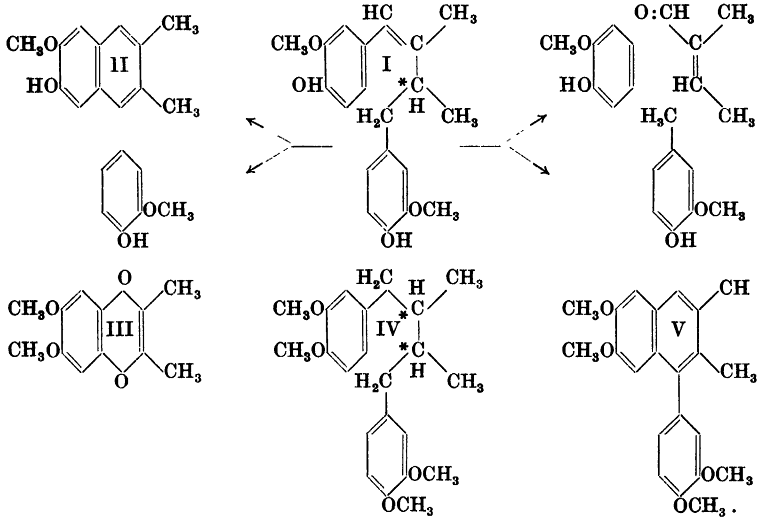
Coniferyl alcohol

Olivil

Tsugaresinol

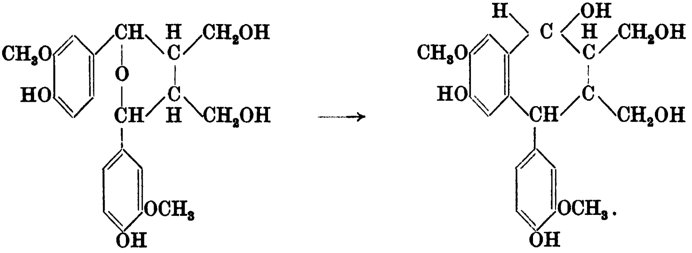
The natural products contain two aromatic components which are almost always derived from guaiacol. These components are combined through a chain of 6 C-atoms which is sometimes cyclised to a tetralin-ring, as is shown by the oxidative degradation of the dimethyl ether to 2 mol. veratric acid, m.p. 179° (compound with open chain) or to 6-veratroyl-veratric acid, m.p. 223° (derivative of tetralin). Ready conversion to the stable tetralin or naphthalene ring system is a common feature of the open-chain compounds.

The constitution of **guaiaretic acid** (I), $C_{20}H_{24}O_4$, m.p. 100·5°, $[\alpha]_D - 94°$, the principal constituent of guaiacum resin, has been determined essentially from the products of its thermal decomposition: viz., pyroguaiacin (2:3-dimethyl-6-hydroxy-7-methoxy-naphthalene) (II), $C_{13}H_{14}O_2$ (methyl ether m.p. 150°) and guaiacol (pyrocatechol monomethyl ether) $C_7H_8O_2$, on the one hand, and guaiacol, guaiol (tiglic aldehyde) and creosol (4-hydroxy-3-methoxy-toluene) on the other:



The structure of pyroguaiacin was established by oxidation of its methyl ether with CrO_3 to 2:3-dimethyl-6:7-dimethoxy-1:4-naphthaquinone (III), $C_{14}H_{14}O_4$, a yellow substance m.p. 242°, and by the formation on Zn dust distillation of guajene (2:3-dimethyl-naphthalene), $C_{12}H_{12}$, m.p. 104° (picrate m.p. 124°); see *Herzig* and *Schiff*, Mo. **19**, 95; synthesis: *Schroeter*, *Lichtenstadt* and *Irineu*, Ber. **51**, 1591. It is thus 2:3-dimethyl-6-hydroxy-7-methoxy-naphthalene, and its formation is reminiscent of the conversion of phenyl-butadiene into naphthalene under the same conditions. The above formula for guaiaretic acid receives further support from the following fact: when its dimethyl ether, $C_{22}H_{28}O_4$, m.p. 95°, $[\alpha]_D - 92°$, is catalytically hydrogenated with Ni in tetralin, or reduced with Na and alcohol, two isomeric hydro-compounds (IV) are obtained; one is optically active, m.p. 87°, $[\alpha]_D - 27°$, the other is inactive, m.p. 101°; this can only be explained by the formation of a new centre of asymmetry. Confirmation of the truth of formula (I), which was based on these results, is given by the ring-closure of the dimethyl ether of guaiaretic acid on dehydrogenation with iodine to the optically inactive naphthalene derivative, dehydro-guaiaretic acid dimethyl ether (V), $C_{22}H_{24}O_4$, m.p. 179° (idem, ibid. 1587).

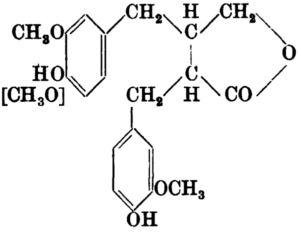
Olivil, $C_{20}H_{24}O_7$, from the olive resin of *Olea europaea* (*Reinitzer*, Mo. **45**, 87), occurs in two forms, amorphous m.p. 66–70°, and sphaero-crystalline, m.p. 142·5° (hydrate m. p. 105°; alcoholate m.p. 120°). With dilute acids it undergoes ring closure to iso-olivil, m.p. 167° (*Vanzetti*, Mo. **52**, 163; C. 1934 II 1313):



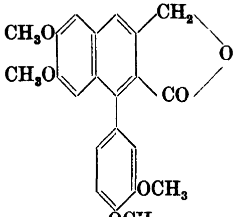
The above structure has been deduced from the oxidation of olivil dimethyl ether, m.p. 156°, to veratric acid and veratroyl-formic acid, and of iso-olivil dimethyl ether, m.p. 184·5°, to veratroyl-veratric acid (*Vanzetti* and *Dreyfuss*, Gazz. **64**, 381), and to the lactone, $C_{22}H_{20}O_6$, m.p. 254° (see formula II, under matairesinol) (*Vanzetti*, C. 1935 II 60; *Dreyfuss*, Gazz. **66**, 96).

Matairesinol $C_{20}H_{22}O_6$ (I), m.p. 117–118° from acetic acid, 74–76° from alcohol, $[\alpha]_D$ — 48·6° (acetone), has been isolated from the wood of *Podocarpus spicatus Matai* (*Easterfield* and *Bee*, J. **97**, 1028). Its constitution has been elucidated by the oxidation of its dimethyl ether, m.p. 128°, with Pb tetracetate to two isomeric lactones of the naphthalene series, $C_{22}H_{20}O_6$ (II), m.p. 254–255° (synthesis: *Haworth* and *Sheldrick*, Canad. J. Res. **12** [1935] 554), and (III), m.p. 215–216° (synthesis: *Haworth* and *Richardson*, J., **1935**, 633, *Haworth*, *Richardson* and *Sheldrick*, J. **1935**, 1576; **1936**, 725). The position of the free phenolic hydroxyls is shown by the degradation of the diethyl ether to 3-methoxy-4-ethoxy-benzoic acid:

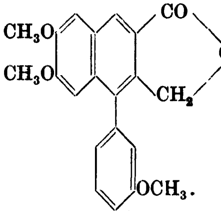
(I)



(II)



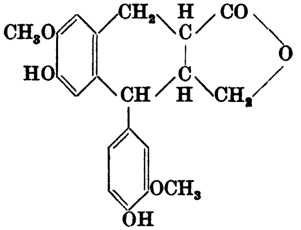
(III)



The glycoside **arctiin** $C_{27}H_{34}O_{11} \cdot H_2O$, m.p. 112°, $[\alpha]_D$ — 38·8°, from the seeds of the burdock, *Arctium Lappa*, gives on hydrolysis the free resin-lactone arctigenin $C_{21}H_{24}O_6$, m.p. 102°, $[\alpha]_D$ — 29·69°, which is a monomethyl ether of matairesinol (see *Haworth* and *Kelly*, J. **1936**, 998) (p. 363).

Tsugaresinol, *conidendrin*, $C_{20}H_{20}O_6$, m.p. 256° (decomp.), $[\alpha]_D$ — 54·8° (acetone) (*diacetate* m.p. 221–222°), forms the chief constituent of the resin from the wood of *Picea excelsa* (*Holmberg*, C. 1927 II 2301); it is identical with the sulphite-liquor lactone discovered by *Tollens* in 1892 (*Lindsey* and *Tollens*, Ann. **267**, 353), and with the tsuga resin acid from the Japanese hemlock (*Kawamura*, C. 1932 II 60; see *Emde* and *Schartner*, Helv. **18**, 344).

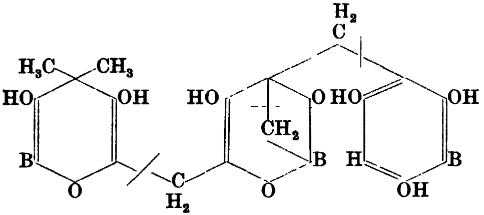
Treatment with alkali gives the corresponding tsugic acid, $C_{20}H_{22}O_7$, m.p. 208–210° (*Holmberg*, Ber. **54**, 2389; *Holmberg* and *Sjöberg*, Ber. **54**, 2406). The oxidation of the dimethyl ether lactone, m.p. 181° (*Erdtman*, Ann. **503**, 283) to veratroyl-veratric acid (synthesis: *Haworth* and *Mavin*, J. **1931**, 1356) shows that the aromatic nuclei are attached through a ring; its dehydrogenation with Pb tetracetate leads to the dehydro-lactone, $C_{22}H_{20}O_6$, m.p. 215–216° (formula III, under matairesinol) (*Haworth* and *Sheldrick*, J. **1935**, 636; *Erdtman*, Ann. **513**, 229). These reactions lead to the following formula for tsugaresinol (the sulphite-liquor lactone):



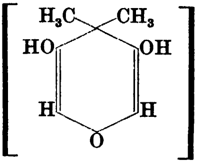
The two isomeric podophyllins, $C_{22}H_{22}O_8$, **podophyllotoxin**, m.p. 117°, and **picropodophyllin**, m.p. 228°, obtained from *Podophyllum* roots, a North American and northern Indian species of *Berberidaceae*, the phenolic components of which differ somewhat from the previous members of this group (see formulae, p. 493), are dealt with under the Poisons because of their physiological properties.

The tannin substances of the fern, the bitter substances of hops, the usnic acids and the catechins are derived from phloroglucinol.

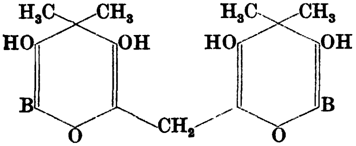
Some of the tannin substances obtained from the extract of the fern *Filix mas* are shown below:



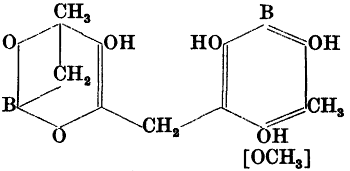
Filicic acid



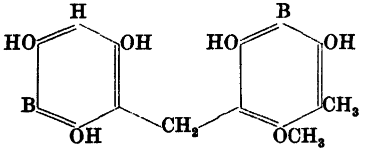
Filicinic acid



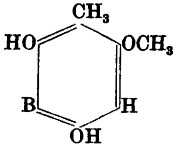
Albaspidin



Flavaspidic acid [Aspidin]



Phloraspin



Aspidinol

(in all formulae B = —CO·C_3H_7).

Filicic acid, $C_{35}H_{38}O_{12}$, m.p. 185°, is a pale-yellow substance, which shows phenolic and ketonic properties. Preliminary experiments in the degradation of the molecule, such as potash fusion, gave *phloroglucinol* and butyric acid; permanganate oxidation led to dimethylmalonic acid, butyric acid and isophthalic acid. Reduction with Zn and alkali, however, gave a clearer insight into the complex structure of the molecule; ten hours' treatment removed all the butyryl-residues and split up the molecule as shown (see formula above):

——— to phloroglucinol $C_6H_6O_3$, m.p. 212°, 1:3:5-trimethylphloroglucinol $C_9H_{12}O_3$, m.p. 184°, and filicinic acid, $C_9H_{10}O_3$, m.p. 215°;

. . . . to methyl-phloroglucinol $C_7H_8O_3$, m.p. 214°, 1:3-dimethyl-phloroglucinol, $C_8H_{10}O_3$, m.p. 163°, and filicinic acid (synthesis: *Robertson* and *Sandrock,* J. **1933**, 1617),

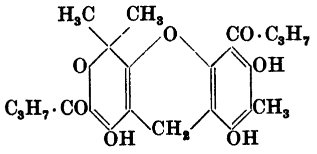
together with three mol. of butyric acid. Reaction for a shorter time gives a much better yield of the homologues of phloroglucinol, two mol. of butyric acid and butyro-filicinic acid $C_{13}H_{16}O_4 \cdot H_2O$, m.p. 67°, anhyd. 97°. The latter gives a mono-azo-compound, m.p. 137°, and a pyrazole derivative, and longer treatment with Zn and alkali converts it also into filicinic acid and butyric acid. Filicinic acid (see formula above) gives a diacetate $C_{12}H_{14}O_5$, m.p. 85°, and a bis-azobenzene-compound, m.p. 209°; its constitution is clear from its degradation with bromine and alkali via 1:1-dimethyl-2:4:6-cyclohexane-trione-3:5-tetrabromide, $C_8H_6O_3Br_4$, m.p. 139°, to CO_2 and a bromo-ketone $C_7H_6O_2Br_6$, m.p. 150°, which has the structure:

$$(CBr_3 \cdot CO)_2C(CH_3)_2,$$

(*Böhm,* Ann. **307**, 250; **318**, 230). The action of alcohol upon filicic acid for some days produces phloroglucinol-butanone $C_{10}H_{12}O_4$, and

Albaspidin, $C_{25}H_{32}O_8$, m.p. 148°, which gives a bis-pyrazole compound with hydrazine since the group (HO)C:C·CO occurs twice in its molecule. The same reduction process employed for filicic acid yields two mol. of filicinic acid, and two mol. of butyric acid, with a little 1:1:3-trimethylphloroglucinol $C_9H_{12}O_3$, m.p. 165–172° (see formula, p. 398); in a similar way, benzene diazonium chloride yields 2 mol. of a filicinic-mono-azo-compound. The formula given above for albaspidin has been proved by its synthesis from butyrofilicinic acid and formaldehyde (*Böhm,* Ann. **302**, 187; **318**, 230).

Flavaspidic acid, $C_{24}H_{28}O_8$, m.p. 156°, a lemon-yellow substance, gives by the same fission with Zn and alkali butyrofilicinic acid, 1:3-dimethylphloroglucinol and butyric acid; under more energetic conditions the products are 1:3:5-trimethyl-phloroglucinol, methyl-phloroglucinol and two mol. of butyric acid, corresponding to the formula given above (see p. 398). HI in acetic acid in addition to opening the 4-ring, brings about ring closure to dihydro-flavaspidic-xanthene $C_{24}H_{28}O_7$, m.p. 260°:



1-Methyl-phloroglucinol-3-butanone $C_{11}H_{14}O_4$, m.p. 162°, is also formed (idem, ibid.).

Aspidin, $C_{25}H_{30}O_8$, m.p. 125°, has been shown to be the monomethyl ether of flavaspidic acid by an analogous fission to methyl-filicinic acid, 1-methylphloroglucinol-2-monomethyl ether $C_8H_{10}O_3$, m.p. 119°, and butyric acid, and by its conversion into the xanthene derivative, m.p. 260° (*Böhm,* Ann. **302**, 187; **329**, 321).

Phloraspin, $C_{23}H_{28}O_8$, m.p. 211°, has been allotted the constitution shown on p. 388 because of its fission into 1-methyl-phloroglucinol-3-butanone and its 2-methyl ether (*Böhm*, Ann. **329**, 338).

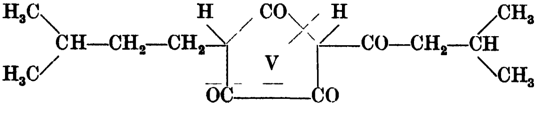
Aspidinol, $C_{12}H_{16}O_4$, m.p. 151°, is identified as the 2-monomethyl ether of 1-methyl-phloroglucinol-5-butanone for the following reasons. Energetic reduction gives 1-methyl-phloroglucinol-2-methyl ether and butyric acid. Its formaldehyde condensation product, $C_{25}H_{32}O_8$, m.p. 191°, gives under the same conditions 2 mol. of butyric acid, 1-methyl-phloroglucinol-2-methyl ether, m.p. 119°, and 1:3-dimethyl-phloroglucinol-2-methyl ether, m.p. 150° (*Böhm*, Ann. **302**, 187; **318**, 245; **329**, 286; synthesis: *Karrer* and *Widmer*, Helv. **3**, 392; *Robertson* and *Sandrock*, J. **1933**, 819).

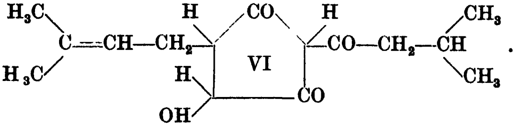
The resin of the hop, *Humulus lupulus*, yields two bitter acids, *humulone* and *lupulone.*

Humulone (I, p. 401), $C_{21}H_{30}O_5$, yellow crystals of m.p. 55°, $[\alpha]_D - 232°$, is attacked by permanganate and gives a tetrabromide. Three of its oxygen atoms can be shown to be present in hydroxyl groups by the Zerewitinoff estimation; they are enolic, giving yellow alkali salts and a red-violet colouration with ferric chloride. Carbonyl reagents have no action on humulone. Catalytic reduction yields a yellow compound, known as humulo-hydroquinone (II), $C_{16}H_{24}O_5$, m.p. 125° (tetrabenzoate m.p. 168°), isopentane, C_5H_{12}, b.p. 27°, being lost from the aromatic nucleus; of the six hydrogen atoms taken up, two are necessary for the fission, and the other four combine with the hydroquinone molecule and the side-chain that has been split out. Humulo-hydroquinone is readily oxidised by atmospheric oxygen to the corresponding humulo-quinone (III), $C_{16}H_{22}O_5$, red needles m.p. 64°; with alkali, this undergoes a sort of benzilic acid rearrangement in which the ring becomes smaller and CO_2 is lost; the product is dihydrohumulic acid (IV), $C_{15}H_{24}O_4$, m.p. 126°. The action of hypobromite on the quinone is similar, and also gives a cyclopentane derivative, isohumulic acid (V), $C_{15}H_{22}O_4$, m.p. 143°, an isomer of humulic acid (VI), m.p. 93°; the latter is produced by the action of alkali upon humulone itself, together with isobutyraldehyde and acetic acid, the products of hydrolysis of the unsaturated side-chain already mentioned. The position of the ten carbon atoms still unaccounted for in humulone was shown by the alkali fission of isohumulic acid (V) (*Wieland*, Ber. **58**, 2012), which was known to be a 1:3:4-cyclopentane-trione derivative; this took place in two directions (see formula), and gave

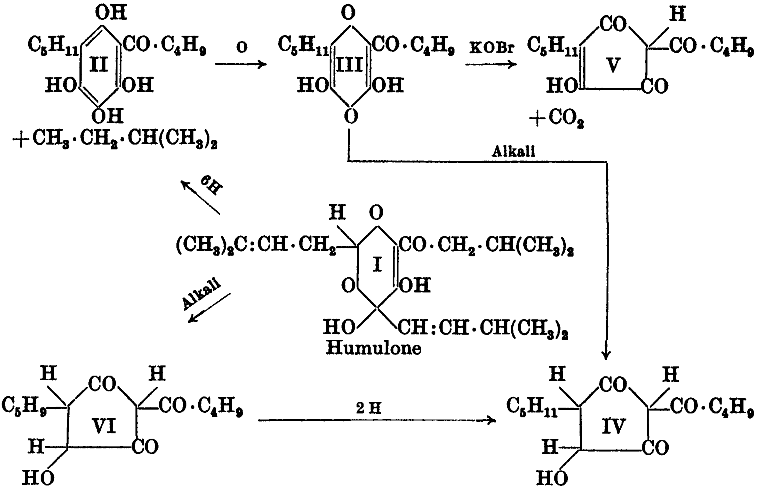
—— methyl-isobutyl-ketone, isoheptanoic acid and oxalic acid
.... methyl-isohexyl-ketone, isovaleric acid and oxalic acid.

Since one of the alkyl residues of humulic acid gives acetone by ozonolysis (*Wieland* and *Martz*, Ber. **59**, 2352), the following formulae are given to isohumulic acid (V) and humulic acid (VI):

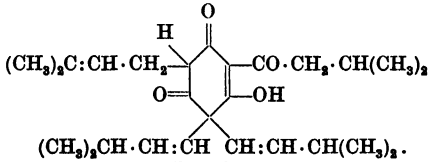




In dihydro-humulic acid (IV), the side-chain is reduced. To sum up, the two more important degradations of humulone (I) can be represented as follows (*Wollmer*, Ber. **49**, 780; *Wieland*, Ber. **58**, 102):



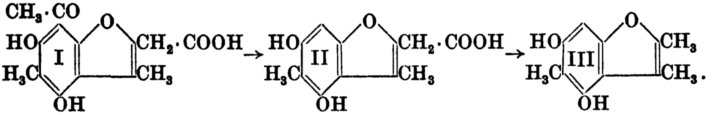
Lupulone, $C_{26}H_{38}O_4$, m.p. 92°, is unsaturated, like humulone; it adds on bromine and immediately decolourises permanganate. It likewise has the properties of a keto-enol. Determination of its constitution has been considerably simplified by its conversion into known derivatives of humulone by the following reactions. Like humulone, lupulone is catalytically hydrogenated, eight atoms of hydrogen being taken up; isopentane, C_5H_{12}, b.p. 27°, is split out, with the formation of a phloroglucinol derivative $C_{21}H_{34}O_4$ (tribenzoate m.p. 165°), which in the free state is very sensitive to air. Its oxidation with oxygen leads to tetrahydrohumulone $C_{21}H_{34}O_5$, m.p. 84°, which behaves as a quinol: the phloroglucinol derivative is reformed by reduction by Clemmensen's method. Alkaline fission of tetrahydrohumulone gives similarly a cyclopentane-derivative, dihydrohumulic acid (see p. 400), a side-chain breaking off as isocaproic acid. Hence in the catalytic hydrogenation of lupulone, one mol. of hydrogen is used for the fission of an isoamylene residue, and one mol. is used for the saturation of each of the three olefinic side-chains. The reactions of lupulone can be expressed by the following formula (*Wollmer*, Ber. 49, 780; 58, 672):



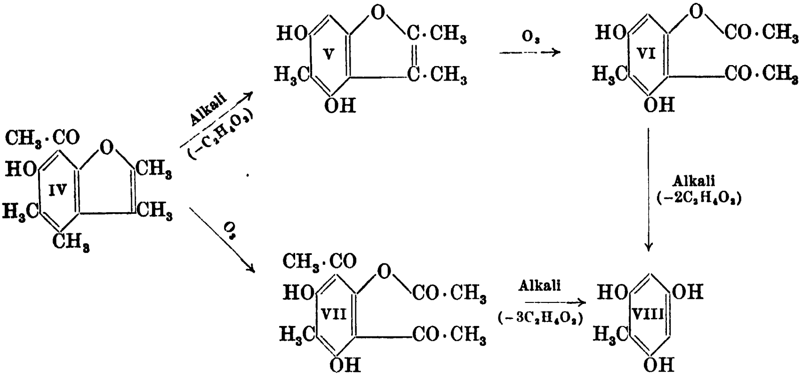
Lupulone

Usnic acid, $C_{18}H_{16}O_7$, a yellow substance m.p. 204°, $[\alpha]_D + 49{\cdot}2°$ ($CHCl_3$), from the lichen *Usnea barbata* and others, is shown to be a derivative of acetoacetic ester by acid hydrolysis to acetone, CO_2 and usnetic acid, $C_{14}H_{14}O_6$, m.p. 210°, and by its decarboxylation (ketonic hydrolysis) to decarbo-usnic acid, $C_{17}H_{18}O_6$, m.p. 178° (*Schöpf* and *Heuck,* Ann. **459**, 233).

Further degradation of usnetic acid (I) yielded derivatives of phloroglucinol, the constitutions of which were established by synthesis. The action of hot conc. caustic potash removes an acetyl group, to give pyro-usnic acid (II), $C_{12}H_{12}O_5$, m.p. 200° (decomp.), which is decarboxylated in high vacuum at 200° to give usneol (III), $C_{11}H_{12}O_3$, m.p. 179° (synthesis: *Curd* and *Robertson*, J. **1933**, 714):



The decarboxylation product of usnetic acid, usnetol (IV), $C_{13}H_{14}O_4$, a yellow compound m.p. 179° (synthesis: idem, ibid., 1173), can be converted by alkali fission and ozonisation, or vice versa, via the intermediates (V) (usneol) and (VI), or (VII), into methyl-phloroglucinol (VIII), $C_7H_8O_3$, m.p. 212° (synthesis: idem, ibid., 437) A tentative formula for usnic acid has been given by *Schöpf* and *Heuck*, Ann. **459**, 233.



The **catechin-tannins,** which are widely distributed throughout the plant kingdom, are mixtures of various products of the condensation of the catechins (flavanol derivatives) (*Freudenberg* and *Maitland*, Ann. **510**, 193).

The constitutions of the fundamental compounds of this group have been determined by degradation and fission (cf. ordinary or gambia catechin, p. 403), and are confirmed by their preparation from synthetic anthocyanidin pigments (*Freudenberg*, *Fikentscher*, *Harder* and *Schmidt*, Ann. **444**, 135; *Freudenberg*, *Carrara* and *Cohn*, Ann. **446**, 87; *Freudenberg* and *Kammüller*, Ann. **451**, 209; *Freudenberg* and *Maitland*, Ann. **510**, 193). The artificial products, as would be expected, show a tendency towards autocondensation, which is greater the smaller the number of hydroxyl groups present: 3:5:7:3′:4′-pentahydroxy-flavane (ordinary catechin) < 3:7:3′:4′-tetrahydroxy-flavane (quebracho-catechin) < 7:3′:4′-trihydroxy-flavane. A possible principle underlying the condensation of the catechins to tannins is given by *Freudenberg* and *Maitland* (Ann. **510**, 193).

It is significant from a biochemical point of view that the catechins and the corresponding flavonols occur together in the same plants; e.g. quebracho-catechin and fisetin, catechin and quercetin, and pistazia-catechin and myricetin (*Freudenberg*, *Fikentscher*, *Harder* and *Schmidt*, Ann. **444**, 135).

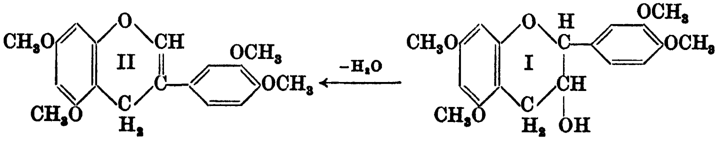
Quebracho-tannin has as its basis quebracho-catechin, $C_{15}H_{14}O_5$ (7:3′:4′-trihydroxy-flavanol-3); the phenolic components of this, resorcinol and pyrocatechol, are obtained by fusion with potash. Their mode of combination is shown by the reduction of fisetinidin (synthesised from ω:3:4-triacetoxy-acetophenone and resorcyl-aldehyde with HCl gas) to *dl*-epi-quebracho-catechin, m.p. 93–96° (acetate m.p. 184–186°), which by rearrangement gives *dl*-quebracho-catechin (acetate m.p. 144–146°) (*Freudenberg* and *Maitland*, Ann. **510**, 193).

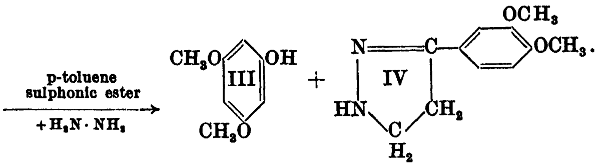
Catechins, $C_{15}H_{14}O_6$:

d-Catechin, m.p. 132°, anhyd. 175°, [α]D + 16·9° (acetone), in gambia catechin from *Uncaria Gambir*; in the cola nut (*Freudenberg* and *Öhler*, Ann. **483**, 140); in rhubarb (*Freudenberg, Böhme* and *Purrmann*, Ber. **55**, 1734).	*d-Epi-catechin*, m.p. 245°, [α]D + 69° (alc.).
l-Catechin, m.p. 95°, anhyd. 175°, [α]D — 16·7° (acetone).	*l-Epi-catechin*, m.p. 245°, [α]D — 68° (alc.), in catechu from *Acacia catechu* (*Freudenberg* and *Purrmann*, Ber. **56**, 1185); in the cola nut (*Freudenberg* and *Öhler*, Ann. 483, 140); in *Thea sinensis* (*Freudenberg* and *Purrmann*, Ann. **437**, 274); in the cocoa bean (*Adam, Hardy* and *Nierenstein*, Am. **53**, 727; *Freudenberg, Cox* and *Braun*, Am. **54**, 1913).
dl-Catechin, m.p. 165°.	*dl-Epi-catechin*, m.p. 169°.

Of the isomeric **catechins** $C_{15}H_{14}O_6$ (5:7:3′:4′-tetrahydroxy-flavanol-3), the properties of which are shown in the above table, only *d*-catechin and *l*-epi-catechin occur in nature.

The first fission of catechin was carried out by potash fusion, and yielded phloroglucinol, protocatechuic acid and pyrocatechol (*Freudenberg* and *Vollbrecht*, Ann. **429**, 284). The type of union of the aromatic nuclei was shown by the energetic reduction of catechin tetramethyl ether with Na and alcohol, followed by methylation; this yielded pentamethoxy-αγ-diphenylpropane (*Freudenberg* and *Cohn*, Ber. **56**, 2127), which was identical with the synthetic product from the corresponding chalkone. That it is an α-phenyl-benzopyrane derivative is proved conclusively by its formation from compounds of the anthocyanidin and flavonol series (*Freudenberg, Fikentscher, Harder* and *Schmidt*, Ann. **444**, 135; *Freudenberg, Carrara* and *Cohn*, Ann. **446**, 87; *Freudenberg* and *Kammuller*, Ann. **451**, 209; see also p. 442). A study of the cis-trans-isomerism of the catechins gave an explanation for the interesting rearrangements and fissions which have been observed. Epi-catechin tetramethyl ether (cis-form) yields with dehydrating agents the tetramethyl ether of flavene (2:3-anhydro-catechin which would be expected); the constitution of the latter has been established by reduction and methylation to the pentamethoxy-αγ-diphenylpropane already mentioned (*Freudenberg, Fikentscher* and *Wenner*, Ann. **442**, 309). The dehydration of the trans-form (catechin tetramethyl ether, I), however, leads to the isoflavene tetramethyl ether (II) (probably with intermediate fission), which has been synthesised from acetyl-phloroglucino-aldehyde dimethyl ether and homoveratric aldehyde; on reduction and methylation it gives the corresponding pentamethoxy-αβ-diphenylpropane (*Freudenberg, Carrara* and *Cohn*, Ann. **446**, 87). The *p*-toluenesulphonic ester of epi-catechin tetramethyl ether is converted by hydrazine into $\Delta^{2:3}$-flavene; under these conditions the isomeric ester of the methylated trans-form breaks down into phloroglucinol dimethyl ether (III) and [3′:4′-dimethoxy]-3-phenyl-4:5-pyrazoline (IV) (see *Freudenberg, Orthner* and *Fikentscher*, Ann. **436**, 286; *Freudenberg* and *Fikentscher*, Ann. **440**, 36; *Freudenberg, Fikentscher* and *Wenner*, Ann. **442**, 309):





When treated with acids, the catechins are converted, more or less readily, into the *phlobaphenes* which are coloured products of high molecular weight (*Bergmann* and *Pojarlieff*, N. **18**, 1114).

Tea-tannin, $C_{22}H_{18}O_{10}$, m.p. 253°, $[\alpha]_D^{23}$ — 177·5° (alcohol) (*Tsujimura*, Sci. Papers Inst. Phys. Chem. Res. Tokyo **26** (1935), 186), has been proved to be galloyl-catechin (cf. *Freudenberg* and *Öhler*, Ann. **483**, 140). Its heptamethyl ether $C_{29}H_{32}O_{10}$, m.p. 140°, $[\alpha]_D$ — 135° (acetone), is oxidised by permanganate to the trimethyl ether of gallic acid, m.p. 167°, and veratric acid, m.p. 175°. The synthetic product prepared from catechin tetramethyl ether and the trimethyl ether of galloyl chloride is identical in physical properties with the heptamethyl ether of the natural product. Demethylation of this synthetic product gives a white amorphous substance, which turns red in the air like natural tea-tannin (*Deuss*, Rec. **42** (1923), 496; *Tsujimura*, loc. cit. **14**, 63; **15**, 155).

Pistazia-tannin gives phloroglucinol and pyrogallol when fused with potash, which shows that the unit of its structure is 5:7:3′:4′:5′-pentahydroxy-flavanol-3. The fact that it occurs in nature together with myricetin (5:7:3′:4′:5′-pentahydroxy-flavonol-3) supports this view (*Freudenberg*, *Fikentscher*, *Harder* and *Schmidt*, Ann. **444**, 135).

III. THE ACTIVE PRINCIPLES OF THE PEPPERS

The pepper-like taste of this class of natural products seems to depend on the presence in the molecule of an amide linking between an amine and a carboxylic acid which is usually unsaturated. Undecenoic acid, isodecenoic acid (in capsaicin), n-decanoic acid and n-nonanoic acid have the strongest effect among the fatty acids (*Nelson*, Am. **41**, 2121; *Széki*, Arch. Pharm. **268** (1930), 151); active fatty-aromatic acids are piperonyl-acrylic acid (in fagaramide) and piperic acid (in piperine) (cf. also *Asano* and *Nakatomi*, J. Pharm. Soc. Japan **53** (1933), 36); purely aromatic acids, such as benzoic and naphthoic acids, give amides which are almost tasteless (*Staudinger* and *Schneider*, Ber. **56**, 699). Reduction of the double bonds causes the physiological action to diminish or to vanish (*Ott* and *Zimmermann*, Ann. **425**, 314; *Jones* and *Pyman*, J. **127**, 2588; *Kobayashi*, Sci. Papers Inst. Phys. Chem. Res. Tokyo **6** (1927), 166). The isobutylamine which is the usual amine constituent in natural pepper-substances can be replaced by vanillylamine (cf. capsaicin). The irritant effect is eliminated by methylation of the free phenolic hydroxyl group of vanillylamine; and the amides of p-hydroxybenzylamine have more marked physiological properties than those of the o-substituted compound (*Ott* and *Zimmermann*, loc. cit.). Anilides and fatty-aromatic amides with long side-chains are inactive (*Széki*, Arch. Pharm. **268** (1930), 151). The piperine of natural pepper, which has piperidine as its basic constituent, has a synthetic analogue with a pepper-like taste in the phenyl-pentenoic acid amide of piperazine which resembles pipiderine in structure (*Riccomanni*, Atti R. Accad. Lincei (5) **33** (1924), I, 145).

Spilanthol, $CH_3\cdot(CH_2)_2\cdot CH:CH\cdot CH:CH\cdot(CH_2)_2\cdot CO\cdot NH\cdot CH_2\cdot CH(CH_3)_2$, b.p. 165°/1 mm., the pungent principle of the garden cress *Spilanthes acmella*, can be hydrogenated to tetrahydro-spilanthol $C_{14}H_{29}ON$, m.p. 37°; it is hydrolysed by alcoholic HCl to capric acid (amide m.p. 98°; anilide m.p. 68°) and isobutylamine (*Asahina* and *Asano*, J. pharm. Soc. Japan **1922**, no. 480, 1; synthesis see below). The constitution of the unsaturated acid with two conjugated double bonds (its maleic anhydride adduct has m.p. 168°) follows from the products of its ozonolysis, which are butyric, formic and succinic acids (*Asano* and *Kanematsu*, Ber. **65**, 1602; cf. also idem, J. Pharm. Soc. Japan **1927**, no. 544, 77).

The roots of the African *Anacyclus pyrethrum* yield the stereoisomeric **pellitorin,** $C_{14}H_{25}ON$, m.p. 72°. On hydrolysis it gives isobutylamine (hydrochloride m.p. 174°) and a fatty acid, characterised by its amide, m.p. 35°. Hydropellitorin (= tetrahydrospilanthol), m.p. 36°, has been synthesized from n-capric chloride and isobutylamine (*Gulland* and *Hopton*, J. **1930**, 6; *Asano*, J. Pharm. Soc. Japan **50** (1930), 89).

The irritant substance of *Anacylus pyrethrum* (pellitory of Spain) has been identified as n-undecadienic acid isobutylamide (*Ott* and *Behr*, Ber. **60**, 2284).

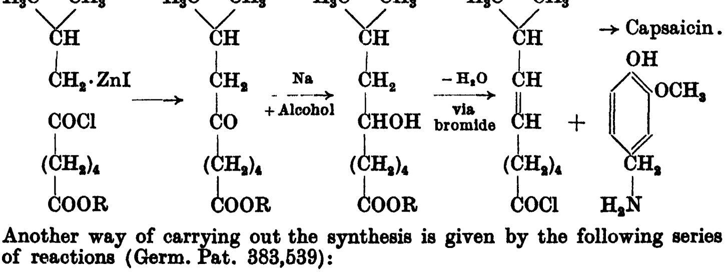
$$C_{10}H_{17}\cdot CO\cdot NH\cdot CH_2\cdot CH(CH_3)_2.$$

It is hydrolysed to isobutylamine (hydrochloride m.p. 174°) and undecadienic acid $C_{11}H_{18}O_2$, b.p. 135°/0·5 mm., which has an unbranched carbon-chain, as is shown by its hydrogenation to n-undecanoic acid $C_{11}H_{22}O_2$, m.p. 28°.

Sanshool, $C_{16}H_{29}ON$, m.p. 51°, has been isolated from *Xanthoxylum piperitum*. Catalytic hydrogenation yields a tetrahydro-derivative $C_{16}H_{33}ON$, m.p. 61° (synthesis: see *Asano*, C. 1922 I 1227), which is hydrolysed by hot HBr into lauric acid, m.p. 51° (p-toluidide m.p. 85°) and isobutylamine (benzoyl derivative, m.p. 57°) (*Asano* and *Kanematsu*, J. Pharm. Soc. Japan **51** (1931), 34).

Capsaicin, $C_{18}H_{27}O_3N$, m.p. 65°, from Spanish pepper (Cayenne pepper) and from paprika (*Capsicum* fruits), is the 3-methoxy-4-hydroxy-benzyl-amide of an isodecenoic acid of the constitution $(CH_3)_2CH\cdot CH:CH\cdot(CH_2)_4\cdot COOH$ (*Nelson*, Am. **41**, 1115). Oxidation of the natural product with $KMnO_4$ gives isobutyric and adipic acids, formed by the break-down of the acid component (*Nelson* and *Dawson*, Am. **45**, 2179). The methyl ether, m.p. 78°, when oxidised in the same way, gives a fatty acid (amide m.p. 99°) and veratric acid, $C_9H_{10}O_4$, m.p. 181°, which contains the carbon skeleton of the aromatic amine (*Lapworth* and *Royle*, J. **115**, 1109). Hydrolysis of capsaicin with acids yields vanillylamine, $C_8H_{11}O_2N$, m.p. 133°, while alkali treatment gives isodecenoic acid, $C_{10}H_{18}O_2$, b.p. 258–261° (dibromide m.p. 59°; amide m.p. 97°); this can be hydrogenated to isocapric acid, $C_{10}H_{20}O_2$, m.p. 25°. When fused with KOH, isodecenoic acid is broken down to iso-octanoic acid and acetic acid, after migration of the double bond (*Nelson*, Am. **42**, 597).

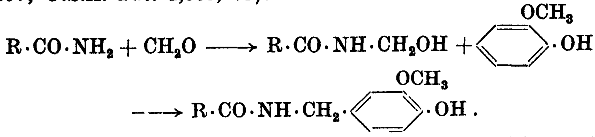
The complete synthesis of capsaicin has been carried out by the following steps (*Späth* and *Darling*, Ber. **63**, 737; cf. *Nelson*, Am. **41**, 2121):



Another way of carrying out the synthesis is given by the following series of reactions (Germ. Pat. 383,539):

Hydroxy-benzaldoxime $\xrightarrow[\text{Pd}]{H_2}$ hydroxy-benzylamine + fatty acid chloride $\xrightarrow[\text{carbonate}]{\text{sodium}}$ amide.

Hydroxy-benzylamides of unsaturated fatty acids can also be prepared from the corresponding methylol-amide and guaiacol (*Einhorn*, etc., Ann. **343**, 207; U.S.A. Pat. 1,503,631):



Fagaramide, $C_{14}H_{17}O_3N$, m.p. 120° (hydrochloride m.p. 137°; see *Goodson*, Biochem. J. **15** (1921), 123), prepared from the root of *Fagara xanthoxyloides*, has been identified as piperonyl-acrylic isobutylamide (*Thoms* and *Thumen*, Ber. **44**, 3717).

Piperine, $C_{17}H_{19}O_3N$, m.p. 128°, discovered by Ørstedt in 1819, is contained to the extent of 6 — 10% in various kinds of Indian pepper (*Piperaceae*). Alcoholic potash decomposes it into piperic acid,

$$(3\!:\!4)CH_2O_2\!:\!C_6H_3\cdot CH\!:\!CH\cdot CH\!:\!CH\cdot COOH,$$

m.p. 217° (the trans-trans-form, see *Ott* and *Eichler*, Ber. **55**, 2653; p-nitrobenzyl ester m.p. 145°, see *Lyons* and *Reid*, Am. **39**, 1727), and piperidine, $C_5H_{11}N$. Piperine can be synthesised by the general methods for the preparation of amides (*Ladenburg* and *Scholtz*, Ber. **27**, 2958; *Scholtz*, Ber. **28**, 1195), likewise its tetrahydro-derivative, $C_{17}H_{23}O_3N$, b.p. 280°/16 mm. (*Borsche*, Ber. **44**, 2942). An artificial pepper-substance, containing the piperidide of phenyl-$\alpha\beta$-(or $\beta\gamma$-)-pentenoic acid, was prepared commercially in large quantities during the World War (*Rosenthaler*, Pharm. Zentr. **67**, 164). The micro-detection of piperine can be carried out by means of its reactions with $CdSO_4$-HCl (idem, C. 1926 II 84), p-dimethylaminobenzaldehyde-sulphuric acid (*Raymond-Hamet*, C. 1926 II 1557), and Reinecke's salt (*Rosenthaler*, Arch. Pharm. **265**, 319), and by its separation as ferro- and ferricyanide (*Cumming* and *Brown*, Chem. and Ind. **47**, 84) or as perchlorate (*Cordier*, Mo. **48**, 535). The slight solubility of the yellow molecular compound, 2 piperine + $SnBr_4$ enables piperine to be separated from the isomer which accompanies it; this is

Chavicine, an oil b.p. 245–260°/0·25 mm. (*Rheinboldt*, Ber. **56**, 1228). Hydrolysis of this compound gives piperidine, but does not lead to chavicic acid (cis-cis-compound, liquid), the acid component of the pepper-substance, which would be expected; as a result of the action of the alkali, isochavicic acid, m.p. 202°, the cis-trans-isomer of isopiperic acid, m.p. 145° is obtained (*Ott* and *Eichler*, Ber. **55**, 2653). The acid (methylene-dihydroxy-phenyl-pentadienic acid) can exist in four stereoisomeric forms, which have been synthesised (*Lohaus*, J. pr. (2) **119**, 235; Ann. **513**, 219; *Lohaus* and *Gall*, Ann. **517**, 278), and their stereoisomerism is shown by their reduction to the same tetrahydro-piperic acid, m.p. 96° (see Vol. III). That chavicine is the cis-cis-form is in agreement with its more intense peppery taste as compared with the trans-trans-form, piperine, a fact which corresponds with the general result that of two geometrical isomers the cis-form is physiologically more active (*Ott* and *Lüdemann*, Ber. **57**, 214).

IV. NATURAL COLOURING MATTERS

Natural colouring matters were known and used even in the most ancient of civilisations. Fabrics dyed with alizarin and indigo have been found in the royal tombs of Egypt, and the art of dyeing with Tyrian purple, the colouring matter obtained from certain Mediterranean shell-fish (*Murex brandaris* and *M. trunculus*), was highly developed in ancient Egypt. The dyestuff saffron was known by the Greeks, and in Roman times the red dye from kermes was used. The discovery of America brought to Europe cochineal and hence carmine as a colouring matter. It is only in the past century that chemical investigation has been able to throw some light upon the constitutions of these organic colouring matters which have been used for thousands of years. The molecular structure of alizarin was elucidated by *Graebe* and *Liebermann* in 1868, and later investigation showed the structures of the other poly-hydroxy-anthraquinones, such as those from madder, the Indian chay-root, rhubarb and aloe. The second half of the 19th century saw the brilliant work of *A. v. Baeyer* on indigo, which led to a technical synthesis of this compound (*Heumann* and *Pfleger*) at the turn of the century. The purple of the ancients was proved to be 6,6′-dibromo-indigo (*Friedländer*, 1902), and it was found that the melanin from animal and plant tissues was also based on the indole molecule. "Indian yellow" was synthesised by *Graebe* and *Neuberg* (1889). Towards the end of the century the pigments of coloured woods (morin, quercetin, haematoxylin, etc.) were investigated in detail, and ten years later the anthocyanins of flowers and fruits were analysed and prepared synthetically (*Karrer*, *Robinson*, and *Willstätter*). The colouring matters of cochineal (carmine, kermes, laccain) were also identified as derivatives of anthraquinone (*Dimroth*). At about the beginning of the 20th century the investigation was begun of the important biological catalysts, chlorophyll and the red blood pigment, the researches of *H. Fischer*, *W. Kuster* and *R. Willstätter* have been successful in bringing to light many important facts. The respiratory enzyme cytochrome, and the enzymes catalase and peroxidase, have also been shown to belong to the porphin series. During this same period the structure of carotenoids was established (*H. v. Euler*, *P. Karrer*, *R. Kuhn*, *R. Willstätter* and *L. Zechmeister*, etc.) and when it was found that carotene was related to the growth-promoting vitamin A, there was a renewed biological interest in this group of compounds. The colouring matters of fungi were identified by *F. Kögl* as derivatives of terphenyl-quinone, anthraquinone and phenanthraquinone. The coloured constituents of most lichens were found to be vulpinic acid and usnic acid. Mention must also be made of the bark pigments, such as those of the coto-bark, and of kawa and curcuma roots. A new class of natural colouring matters was discovered in pyocyanin and chlororaphin, which are derivatives of phenazine, and are obtained from bacteria (*F. Wrede*, *F. Kögl*). The yellow wing-pigment, xanthopterin, of the brimstone-yellow butterfly, and the colourless leucopterin of the cabbage white, contain several purine nuclei (*H. Wieland* and *C. Schöpf*). The lyochromes or flavines, which possess vitamin B_2 activity, are based upon the alloxazine ring system.

(a) POLYENE COLOURING MATTERS (CAROTENOIDS)[1]

The carotenoids were treated briefly in vol. I, and here only the more recent results will be considered. The following table summarises the natural polyenes, their characteristic physical constants (m.p., optical rotation and absorption bands) and their occurrence.

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[1] Literature: **General treatment:** *Willstätter* and *Mieg*, Ann. **355**, 1; *Karrer*, Z. angew. Chem. **42**, 918; **45**, 87; *Winterstein*, ibid. **47**, 315; *Zech-*

meister, N. **20**, 608; *Karrer*, Carotinoide: Handbuch der Biochemie des Menschen und der Tiere, Band 10: Gustav Fischer, Jena, 1933; *Lederer*, Les Caroténoides des Plantes, Hermann et Cie., Paris, 1934; *Zechmeister*, Carotinoide: J. Springer, Berlin, 1934; *Willstaedt*, Carotinoide, Pilz- und Bakterienfarbstoffe: Enke, Stuttgart, 1934; Ann. Reports of the Chemical Society, **1933**, **1935**; **Carotenes**: *Zeise*, Ann. **62**, 380; *Willstätter* and *Mieg*, Ann. **355**, 1; *Zechmeister* and *v. Cholnoky*, Ann. **454**, 54; **455**, 70; Ber. **61**, 566; *Pummerer* and *Rebmann*, Ber. **61**, 1100; *Zechmeister* and *v. Cholnoky*, Ber. **61**, 1534; *v. Euler*, *Karrer* and *Rydbom*, Ber. **62**, 2447; *Pummerer*, *Rebmann* and *Reindel*, Ber. **64**, 492; *Kuhn* and *Lederer*, Ber. **64**, 1349; *Kuhn* and *Brockmann*, ibid, 1859; *Kuhn* and *Lederer*, Ber. **65**, 637; *Kuhn* and *Brockmann*, ibid. 894; idem, Ber. **66**, 407; **67**, 1408; *Willstätter* and *Escher*, Z. physiol. Chem. **64**, 47; *Escher*, ibid. **83**, 198; *Fischer* and *Rose*, ibid. **88**, 331; *Kuhn* and *Lederer*, ibid. **200**, 246; *Kuhn* and *Brockmann*, ibid. 255; *Winterstein* and *Ehrenberg*, ibid. **207**, 25; *Kuhn* and *Brockmann*, ibid. **213**, 1; *Winterstein*, ibid. **215**, 51; *Brockmann*, ibid. **216**, 45; *Winterstein*, ibid. **219**, 249; *Karrer*, Z. angew. Chem. **42**, 923; *Kuhn* and *Lederer*, N. **19**, 306; *Kuhn* and *Brockmann*, N. **21**, 44; *Karrer* and *Helfenstein*, Helv. **12**, 1142; *Karrer*, *Helfenstein* and *Wehrli*, Helv. **13**, 87; *Karrer*, *Helfenstein*, *Wehrli* and *Wettstein*, ibid. 1084; **14**, 614; *Karrer* and *Morf*, ibid. 833; 1033; *Karrer*, *Morf*, *v. Krauss* and *Zubrys*, Helv. **15**, 490; *Karrer*, *Schopp* and *Morf*, ibid. 1158; *v. Euler*, *Karrer* and *Walker*, ibid. 1507; *Karrer* and *Walker*, Helv. **16**, 641; *Karrer*, *Solmssen* and *Walker*, Helv. **17**, 417; *Karrer*, *v. Euler* and *Solmssen*, ibid. 1169; *Karrer* and *Solmssen*, Helv. **18**, 25; *Kuhn*, Swiss Pat. 155,444; Germ. Pat. 567,683. **Lycopene**: *Zechmeister* and *v. Cholnoky*, Ber. **63**, 422; 787; *Zechmeister* and *Tuzson*, ibid. 2881; *Kuhn* and *Grundmann*, Ber. **65**, 898, 1880; *Willstätter* and *Escher*, Z. physiol. Chem. **64**, 47; *Winterstein* and *Ehrenberg*, ibid. **207**, 27; *Karrer* and *Widmer*, Helv. **11**, 751; *Karrer*, *Widmer* and *Helfenstein*, ibid. 1201; *Karrer* and *Bachmann*, Helv. **12**, 285; *Karrer*, *Helfenstein* and *Wehrli*, Helv. **13**, 87; *Karrer*, *Helfenstein*, *Wehrli* and *Wettstein*, ibid. 1084; *Karrer* and *Helfenstein*, Helv. **14**, 78; *Karrer*, *Helfenstein*, *Pieper* and *Wettstein*, ibid. 435; *Karrer* and *Morf*, ibid. 845. **Rubixanthin**: *Kuhn* and *Grundmann*, Ber. **67**, 339. **Kryptoxanthin**: *Kuhn* and *Grundmann*, Ber. **66**, 1746; *Zechmeister* and *Tuzson*, Ber. **67**, 170; *Kuhn* and *Grundmann*, Ber. **67**, 593; *Karrer* and *Schlientz*, Helv. **17**, 55. **Xanthophyll**: *Willstätter* and *Mieg*, Ann. **355**, 1; *Zechmeister* and *v. Cholnoky*, Ann. **481**, 42; *Zechmeister* and *Tuzson*, Ber. **61**, 2003; **62**, 2226; *Zechmeister* and *v. Cholnoky*, Z. physiol. Chem. **189**, 159; *Karrer*, *B. v. Euler* and *H. v. Euler*, C. 1929 I 1590; *Oku*, Bull. Agric. Chem. Soc. Japan **5** (1929), 8; *Escher*, Helv. **11**, 752; *Karrer*, *Salomon* and *Wehrli*, Helv. **12**, 792; *Karrer*, *Helfenstein* and *Wehrli*, Helv. **13**, 87, 268; *Karrer* and *Ishikawa*, ibid. 709; *Karrer* and *Salomon*, ibid. 1063; *Karrer*, *Helfenstein*, *Wehrli* and *Wettstein*, ibid. 1084; *Karrer* and *Ishikawa*, ibid. 1099; *Karrer* and *Jirgensons*, ibid. 1102; *Karrer* and co-workers, Helv. **14**, 629; *Karrer* and *Nilsson*, ibid. 843. **Lutein**: *Kuhn*, *Winterstein* and *Kaufmann*, Ber. **63**, 1489; *Zechmeister* and *Tuzson*, ibid. 2303; *Willstätter* and *Escher*, Z. physiol. Chem. **76**, 214; *Fischer* and *Hess*, ibid. **187**, 133; *Kuhn*, *Winterstein* and *Lederer*, ibid. **197**, 141, 150; *Winterstein* and *Ehrenberg*, ibid. **207**, 26; *Kuhn* and *Winterstein*, N. **18**, 754; *Karrer* and *Helfenstein*, Helv. **13**, 86; *Karrer* and *Salomon*, ibid. 1063; *Karrer* and *Nilsson*, Helv. **14**, 843. **Zeaxanthin**: *Zechmeister* and *v. Cholnoky*, Ann. **478**, 95; **481**, 42; *Pummerer* and *Rebmann*, Ber. **61**, 1099; *Pummerer*, *Rebmann* and *Reindel*, Ber. **62**, 1411; *Zechmeister* and *Tuzson*, ibid. 2226; *Kuhn*, *Winterstein* and *Kaufmann*, Ber. **63**, 1489; *Kuhn* and *Brockmann*, Ber. **66**, 833; *Kuhn* and *Grundmann*, Ber. **67**, 596; *Kuhn*, *Winterstein* and *Kaufmann*, N. **18**, 418; *Zechmeister* and *v. Cholnoky*, Z. physiol. Chem. **189**, 159; *Zechmeister* and *Szilard*, ibid. **190**, 67; *Zechmeister* and *Tuzson*, ibid. **196**, 199; *Kuhn*, *Winterstein* and *Lederer*, ibid. **197**, 145; *Kuhn* and *Smakula*, ibid. 161; *Kuhn* and *Brockmann*, ibid. **206**, 41; *Winterstein* and *Ehrenberg*, ibid. **207**, 27; *Kuhn*

The separation of a complex mixture of carotenoids, chlorophyll, etc., is based upon the differing solubilities of the hydrocarbons, esters and oxygenated carotenoids in high-boiling petroleum ether and in aqueous methanol. A further fractionation can be achieved by the adsorption method of *M. Tswett* and *R. Kuhn* ("chromatographic analysis") (*Kuhn, Winterstein* and *Lederer,* Z. physiol. Chem. **197**, 141; *Kuhn* and *Lederer,* ibid. **200**, 108; *Kuhn* and *Brockmann,* ibid. **213**, 192; *Winterstein,* ibid. **215**, 51; *Kuhn* and *Lederer,* N. **19**, 306; *v. Euler* and *Gard,* C. 1932 I 1544; *Kuhn* and *Winterstein,*

and *Wiegand,* Helv. **12**, 499; *Karrer, Salomon* and *Wehrli,* ibid. 790; *Karrer, Wehrli* and *Helfenstein,* Helv. **13**, 269; *Karrer* and *Wehrli,* ibid. 1104; *Karrer* and *Pieper,* Helv. **14**, 838; *Karrer, Morf, Krauss* and *Zubrys,* Helv. **15**, 490; *v. Euler, Karrer* and *Zubrys,* Helv. **17**, 24; *Karrer, Solmssen* and *Walker,* ibid. 417. **Rhodoxanthin**: *Kuhn* and *Brockmann,* Ber. **66**, 828; *Kylin,* Z. physiol. Chem. **157**, 148; *Kuhn* and *Brockmann,* ibid. **213**, 192; *Prat,* Biochem. Z. **152**, 495; *Karrer* and *Solmssen,* Helv. **18**, 477; *Montevarde* and *Lubimenko,* C. 1914 I 1093; *Lipmaa,* C. r. **182**, 867; Ber. deut. bot. Ges. **44** (1926), 643; *Kylin,* Z. physiol. Chem. **163**, 229. **Flavoxanthin**: *Kuhn* and *Brockmann,* Z. physiol. Chem. **213**, 192. **Violaxanthin**: *Zechmeister* and *Cholnoky,* Ann. **481**, 42 *Kuhn* and *Winterstein,* Ber. **64**, 328 *Zechmeister* and *Cholnoky,* Z. physiol. Chem. **189**, 159; **208**, 26; *Karrer* and *Morf,* Helv. **14**, 1044; *Karrer* and *Notthafft,* Helv. **15**, 1195; *Karrer* and *Solmssen,* Helv. **19**, 1024. **Taraxanthin**: *Kuhn* and *Lederer,* Z. physiol. Chem. **200**, 108; **213**, 188; *Karrer* and *Salomon,* Helv. **13**, 1063; *Karrer* and *Morf,* Helv. **15**, 863. **Fucoxanthin**: *Willstätter* and *Page,* Ann. **404**, 237, 253; Ber. **47**, 2831; *Kuhn* and *Winterstein,* Ber. **64**, 330; *Karrer, Wehrli* and *Helfenstein,* Helv. **13**, 271; *Karrer* and co-workers, Helv. **14**, 622. **Capsanthin**: *Willstätter* and *Mieg,* Ann. **355**, 1; *Willstätter* and *Page,* Ann. **404**, 237; *Zechmeister* and *v. Cholnoky,* Ann. **454**, 54, 70; **455**, 70; **465**, 289; **478**, 95; **487**, 197; **489**, 1; **509**, 269; *Karrer* and co-workers, Helv. **14**, 625; *Karrer* and *Hübner,* Helv. **19**, 474. **Astacene**: *Karrer, Loewe* and *Hübner,* Helv. **18**, 96; *Karrer* and *Hübner,* Helv. **19**, 479; *Karrer* and *Loewe,* Helv. **17**, 745; *Willstaedt,* Svensk Kem. Tidskr., **46** (1934), 205; *Lederer,* C. r. Soc. Biol. **117** (1934), 1086; **118** (1935), 542. **Azafrin**: *Liebermann,* Ber. **44**, 850; *Liebermann* and *Schiller,* Ber. **46**, 1973; *Liebermann* and *Mühle,* Ber. **48**, 1653; *Kuhn, Winterstein* and *Roth,* Ber. **64**, 333; *Kuhn* and *Deutsch,* Ber. **66**, 883; *Kuhn, Winterstein* and *Wiegand,* Helv. **11**, 716. **Bixin**: *Herzig* and *Faltis,* Ann. **431**, 40; *Heiduschka* and *Panzer,* Ber. **50**, 549; *Herzig* and *Faltis,* ibid. 927; *Heiduschka* and *Panzer,* ibid. 1525; *Kuhn* and *Winterstein,* Ber. **65**, 646; *Kuhn* and *Drumm,* ibid. 1459; *Kuhn, Drumm, Hoffer* and *Möller,* ibid. 1785; *Kuhn* and *Winterstein,* Ber. **65**, 1873; *Herzig* and *Faltis,* Mo. **35**, 997; *Karrer, B. v. Euler* and *H. v. Euler,* C. 1929 I 1590; *Waldmann* and *Brandenburger,* Z. Krist. **82**, 77; *Kuhn* and *Winterstein,* Helv. **11**, 427; *Kuhn, Winterstein* and *Wiegand,* ibid. 716; *Kuhn, Winterstein* and *Karlovitz,* Helv. **12**, 64; *Karrer* and co-workers, Helv. **12**, 743; *Kuhn* and *Ehmann,* ibid. 904; *Karrer* and co-workers, Helv. **15**, 1399; *Karrer* and *Takahashi,* Helv. **16**, 287; *Karrer* and *Benz,* Helv. **16**, 337; *van Hasselt,* Rec. **30**, 1; **33**, 192; *Rinkes,* Rec. **48**, 603; 1093. **Crocetin**: *Weiss,* J. pr. (2) **101**, 65; *Kuhn* and *L'Orsa,* Ber. **64**, 1732; *Kuhn, Drumm, Hoffer* and *Möller,* Ber. **65**, 1785; *Kuhn* and *Winterstein,* Ber. **66**, 209; *Schmid* and *Kotter,* Mo. **59**, 341; *Karrer* and *Salomon,* Helv. **10**, 397; *Kuhn* and *Winterstein,* Helv. **11**, 126; *Ott,* ibid. 313; *Karrer* and *Salomon,* ibid. 513; 711; *Kuhn, Winterstein* and *Wiegand,* ibid. 716; *Karrer* and *Widmer,* ibid. 751; *Kuhn, Winterstein* and *Karlovitz,* Helv. **12**, 64; *Karrer* and *Miki,* ibid. 985; *Karrer* and *Helfenstein,* Helv. **13**, 392; *Karrer* and *Golde,* ibid. 707; *Karrer* and *Morf,* Helv. **14**, 845; *Karrer* and co-workers, Helv. **15**, 1218, 1399; *Karrer, Benz* and *Stoll,* Helv. **16**, 297. **Vitamin A** (constitution): *Karrer, Morf* and *Schöpp,* Helv. **14**, 1036; *v. Euler* and *Karrer,* ibid. 1040; *Karrer, Morf* and *Schöpp,* ibid. 1431; *v. Euler, Karrer, Klussmann* and *Morf,* Helv. **15**, 502; *Karrer, Morf* and *Schöpp,* Helv. **16**, 557.

Ber. **64**, 326; *Kuhn* and *Lederer*, ibid. 1349; *Koschara*, Ber. **67**, 761; *Karrer*, *Morf* and *Schopp*, Helv. **14**, 1036). For a detailed description of a separation, see *Kuhn* and *Brockmann*, Z. physiol. Chem. **206**, 44; *Winterstein* and *Stein*, ibid. **220**, 247; *Zechmeister* and *Tuzson*, ibid. **225**, 189; *Zechmeister* and *v. Cholnoky*, Ann. **509**, 269.

The quantitative estimation of the pigments is carried out colorimetrically by comparison with standard solutions of bichromate, azobenzene, etc., (*Kuhn* and *Smakula*, Z. physiol. Chem. **197**, 161; *v. Euler*, *Demole*, *Karrer* and *Walker*, Helv. **13**, 1078; *Connell*, Biochem. J. **18** (1924), 1127), and by measurement of the intensity of the absorption bands (*Kuhn* and *Brockmann*, Z. physiol. Chem. **206**, 44).

Methods for determining the structure: A comparison of the physical constants of the n-paraffins with those of branched-chain hydrocarbons gave an indication of structural principles of the aliphatic terpenes (*Kuhn* and *Ehmann*, Helv. **12**, 906; *Kuhn* and *Grundmann*, Ber. **69**, 224). The determination of the molecular refraction (*Karrer*, Z. angew. Chem. **42**, 918), the consideration of the absorption spectrum (*v. Euler*, *Karrer*, *Klussmann* and *Morf*, Helv. **15**, 502), and the colorimetric comparison of the synthetic diphenylpolyenes, polyene-alcohols and carboxylic acids (*Hausser*, *Kuhn* and *Smakula*, Z. physikal. Chem. B. **29** (1935), 384; with *Kreuchen*, ibid. 363; with *Hoffer*, ibid., 371; with *Deutsch*, ibid. 378) with those of the natural products (*Kuhn* and *Winterstein*, Helv. **11**, 427; *Karrer* and *Bachmann*, Helv. **12**, 285; *Kuhn* and *Winterstein*, ibid. 899; *Karrer*, *Morf* and *Schopp*, Helv. **14**, 1036; *Kuhn* and *Hoffer*, Ber. **63**, 2164), confirmed the number and position of the double bonds which were found from the results of catalytic hydrogenation (see below). The presence or absence of optical activity was important for the determination of structural formulae, as in the case of α- and β-carotene (*Kuhn* and *Lederer*, Ber. **64**, 1349). The molecular weights could be determined by the application of the ebullioscopic method, by Rast's method, and by estimation of the equivalents of the polyene-acids (cf. *Kuhn* and *Deutsch*, Ber. **66**, 883); another method is to determine the dimensions of the elementary cell in the crystal by X-ray analysis (e.g. with bixin and crocetin) (see *Kuhn* and *L'Orsa*, Ber. **64**, 1733; *Waldmann* and *Brandenberger*, Z. Krist. **82**, 77). Individual carotenoids can be distinguished from one another by typical colour reactions with conc. sulphuric acid, arsenic trichloride and antimony trichloride (*v. Euler* and *Karrer*, Helv. **15**, 496; *Gillam*, Biochem. J. **29** (1935), 1831).

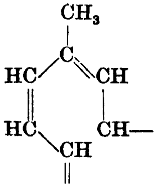
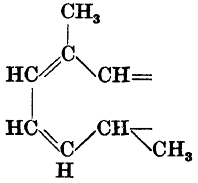
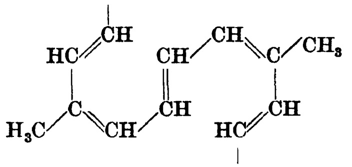
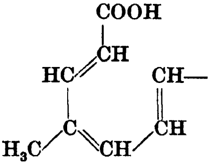
Exhaustive catalytic hydrogenation gives the total number of double bonds (see table, pp. 412 and 413; cf. *Zechmeister*, *v. Cholnoky* and *Vrabély*, Ber. **61**, 566, 1534; *Zechmeister* and *Tuzson*, ibid. 2003; *Karrer* and *Salomon*, Helv. **10**, 397; **11**, 513, 711), and shows whether the molecule is an open chain or has a ring structure (cf. also the results of oxidation).

The oxygen atoms in the phylloxanthins are shown by the Zerewitinoff estimation and by ester formation to be present as alcoholic hydroxyl groups (cf. *Karrer*, *Helfenstein* and *Wehrli*, Helv. **13**, 87, 268; *Karrer* and *Ishikawa*, ibid., 709, 1099; *Karrer* and *Jirgensons*, ibid. 1102), or else to be in the form of ketonic groups (rhodoxanthin: *Kuhn* and *Brockmann*, Ber. **66**, 828). Azafrin, bixin and crocetin are polyene-carboxylic acids.

Polyenes in which the carbonyl groups are conjugated with the carbon double bonds give orange-yellow solutions in petrol ether and pure red solutions in alcohol. Their dihydro-compounds give deeply coloured enolic salts with alkalies, and these have a marked tendency to be oxidised to the original carotenoid by the oxygen of the air (cf. β-carotenone, *Kuhn* and *Brockmann*, Ber. **65**, 894; rhodoxanthin, idem, Ber. **66**, 828; azafrinone methyl ester, *Kuhn* and *Deutsch*, ibid. 883; crocetin dimethyl ester and methylbixin, *Kuhn*, *Drumm*, *Hoffer* and *Möller*, ibid. 1785).

The carbonyl group present in a ring can be reduced with Al-isopropoxide, and in this way two natural xanthophylls, viz. rhodoxanthin and zeaxanthin, were converted into one another for the first time (*Karrer* and *Solmssen*, Helv. **18**, 477). Cf. also the conversion of capsanthin into capsanthol (*Karrer* and *Hübner*, Helv. **19**, 474).

The so-called wet-combustion method of *Kuhn* (oxidation with CrO_3) (*Kuhn* and *L'Orsa*, Z. angew. Chem. **44**, 847) shows the number of branched methyl groups present; one molecule of acetic acid is formed from each methyl group. Their relative positions in the molecule of the polyene was indicated by thermal decomposition,

which yielded toluene, m-xylene (*Zechmeister* and *v. Cholnoky*, Ann. **478**, 95; *Kuhn* and *Winterstein*, Ber. **65**, 1873; **66**, 1733; Helv. **11**, 430), 2:6-dimethyl-naphthalene (idem, Ber. **66**, 429) or toluic acid (idem, Ber. **65**, 646, 1873); it was conclusively proved by the method of successive oxidative degradation and by the synthesis of the completely hydrogenated carotenoids and their hydrogenated fission products (cf. below).

Ozonolysis established the open-chain structure for lycopene, two molecules of acetone (p-nitrophenylhydrazone m.p. 143°) being formed (see *Karrer*, *Helfenstein*, *Pieper* and *Wettstein*, Helv. **14**, 435); β-carotene, vitamin A, etc., gave geronic acid (*semicarbazone* m.p. 163°), which is a proof of the presence of a 6-membered ring (see *Karrer*, *Morf* and *Schöpp*, Helv. **14**, 1039, 1434; *Karrer*, *Morf*, *Krauss* and *Zubrys*, Helv. **15**, 490); bixin yielded methyl-glyoxal (I), β-acetyl-acrylic methyl ester (II) and the methyl ester of the half-aldehyde of methyl-muconic acid (III) (*Rinkes*, Rec. **48** (1929), 1093):

Carotenoid	Formula	╒	M.p.	[α]D	Abs.-Max. (mμ)	Occurrence
α-Carotene	$C_{40}H_{56}$	11	187°	+ 380°	511, 478, 442 (CS_2)	green leaves (stinging nettle, grass, spinach, tea), paprika, mountain ash berries, *Curcurbita*, carrot (*Daucus carota*); *corpus luteum*, ox gallstones, raw silk, mandarins, apricots
β-Carotene	$C_{40}H_{56}$	11	184°	inact.	497, 466, 430 ($CHCl_3$) 520, 485, 454 (CS_2)	
γ-Carotene[1]	$C_{40}H_{56}$	12	178°	inact.	508, 475, 446 ($CHCl_3$) 533, 496, 463 (CS_2)	accompanies α- and β-carotene; fruit of *Convallaria majalis*, *Gonocaryum* species
Lycopene	$C_{40}H_{56}$	13	175°	inact.	517, 480, 453 ($CHCl_3$) 546, 506, 474 (CS_2)	tomato (*Lycopersicum esculentum*), hips, water melon
Rubixanthin	$C_{40}H_{56}O$	12	160°	inact.	533, 495, 462 (CS_2)	hips (*Rosa rubiginosa*), *Calendula off.*
Kryptoxanthin	$C_{40}H_{56}O$	11	169°	inact.	519, 483, 452 (CS_2) 497, 463, 433 ($CHCl_3$)	in the red calices and berries of species of *Physalis*; *Carica Papaya*
Xanthophyll (mixture)	$C_{40}H_{56}O_2$	11	174–188°	+ 137° to + 192°	482, 456, 430 ($CHCl_3$)	green leaves, algae; raw silk
Lutein[2]	$C_{40}H_{56}O_2$	11	193°	[α]D + 72° [α]Cd + 175°	487,5, 456 ($CHCl_3$) 511, 478, 446 (CS_2)	egg-yolk, yellow feather pigment, chief constituent of leafxanthophyll; as dipalmitic ester, "helenien", in the flowers of *Tropaeolum majus*, berries of *Convallaria majalis*
Zeaxanthin	$C_{40}H_{56}O_2$	11	216°	inact.	495, 461, 429 ($CHCl_3$) 520, 484, 452 (CS_2)	the seeds of the spindlewood tree; as dipalmitic ester, "physalien", in maize (*Zea mays*) and various berries (Jerusalem cherry, buckthorn, etc.)
Rhodoxanthin	$C_{40}H_{50}O_2$	12	219°	inact.	546, 510, 482 ($CHCl_3$) 564, 525, 491 (CS_2)	in the chromoplasts of *Thuja*, *Juniperus*, *Equisetum*, *Reseda*, berries of the yew (*Taxus baccata*)
Flavoxanthin	$C_{40}H_{56}O_3$	11	184°	[α]Cd +190°	478, 447,5 420 (CS_2)	common buttercup (*Ranunculus acer*)

Footnotes: see p. 413.

Carotenoid	Formula	╒	M.p.	[α]D	Abs.-Max. (mμ)	Occurrence
Capsanthin[3]	$C_{40}H_{58}O_3$	11	178°	— 70°	491, 455 ($CHCl_3$) 544, 504 (CS_2)	Paprika (*Capsicum annuum*)
Violaxanthin	$C_{40}H_{56}O_4$	10	208°	[α]Cd + 35°	482, 451,5 ($CHCl_3$) 500, 469, 441 (CS_2)	*Viola tricolor* (the pansy)
Taraxanthin	$C_{40}H_{56}O_4$	11	185°	[α]Cd + 200°	501, 468, 439 (CS_2)	flowers of dandelion (*Taraxacum off.*), coltsfoot (*Tussilago farfara*)
Fucoxanthin	$C_{40}H_{56}O_6$	10	160°	+ 72,5°	492, 457 ($CHCl_3$) 492–476, 467–451 (CS_2)	brown algae (*Fucus*)
Astacene[4]	$C_{40}H_{48}O_4$	10	243°	inact.	350–450 (Alcohol) 450–500 (Pyridine)	as dark-brown chromoproteid in the claws of the lobster (*Astacus gammarus*), as red lipochrome in its hypodermis, and as green chromoproteid of the ovoester, m.p. 248°; in the eggs of the crayfish, in goldfish, and in the eggs of the sea-spider
Azafrin	$C_{27}H_{38}O_4$	7	214°	[α]Cd — 75·5°	458, 428 ($CHCl_3$)	*Azafranillo* roots; *Escobedia* species
Bixin	$C_{25}H_{30}O_4$	9	198°	inact.	506, 472, 439 ($CHCl_3$) 518, 488 (CS_2)	*Bixa orellana*
Crocetin I (trans-Form)	$C_{20}H_{24}O_4$	7	273°	inact.	463, 435·5 ($CHCl_3$)	flower of the mullein (*Verbascum thapsus*) and mahogony tree; as digentiobiose ester, gentiobiosemethyl ester and dimethyl ester I, m.p. 222°, II, m.p. 141°, in saffron (*Crocus sativus*); in the fruit of *Gardenia grandiflora*
Crocetin II (cis-Form)	$C_{20}H_{24}O_4$	7	285°	inact.	458, 432·5 ($CHCl_3$)	
Vitamin A	$C_{20}H_{30}O$	5	7–8°	inact.	315, 328, 370 ($CHCl_3$)	in animal organs and products (heart, kidney, liver, butter, eggs, etc.); germ, leaves, fruit and oils of many plants

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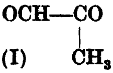
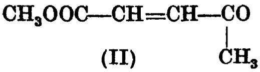
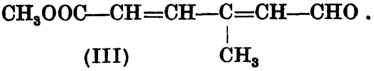
[1] The monocyclic δ-carotene (absorption maxima 503, 470, 440 in $CHCl_3$, 526, 490, 457 in CS_2), with the double bonds in the same positions as in α-carotene, is found in the fruits of *Gynocaryum pyriforme* (*Winterstein*, Z. physiol. Chem. **219**, 249).

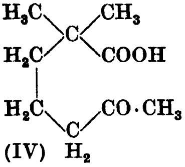
[2] Canary-xanthophyll (abs. 472, 443, 418), from the feathers of the canary (*Serinus canaria*), the oriole, etc., and from the epidermis of the beak

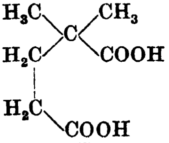

(I)
$OCH{-}\underset{CH_3}{\underset{|}{CO}}$


(II)
$CH_3OOC{-}CH{=}CH{-}\underset{CH_3}{\underset{|}{CO}}$


(III)
$CH_3OOC{-}CH{=}CH{-}\underset{CH_3}{\underset{|}{C}}{=}CH{-}CHO$.

The usual oxidising agents degrade those polyenes which contain an ionone-ring (e.g. carotene, phylloxanthin) either to geronic acid (IV), or else to dimethylglutaric acid (V), dimethylsuccinic acid (VI), or dimethylmalonic acid (VII):


(IV)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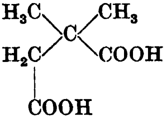
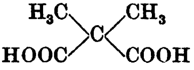

(VI)


(VII)

From the compounds obtained the position of the hydroxyl or carbonyl in the hydroaromatic ring can be inferred (see *Karrer* and *Helfenstein*, Helv. **12**, 1142; *Karrer*, *Helfenstein* and *Wehrli*, Helv. **13**, 268; idem with *Wettstein*, ibid. 1088; **14**, 629; *Karrer* and *Morf*, ibid. 1044; *Karrer*, *Morf* and *Walker*, Helv. **16**, 975; *Pummerer*, *Rebmann* and *Reindel*, Ber. **64**, 492; *Kuhn* and *Deutsch*, Ber. **66**, 883).

The methods which have been mentioned so far involve almost complete destruction of the molecule of the pigment; by using smaller amounts of the oxidising agent under milder conditions, however, derivatives or degradation products of higher molecular weight can be isolated. β-Carotene gives with perbenzoic acid β-carotene oxide, $C_{40}H_{56}O$ (*v. Euler*, *Karrer* and *Walker*, Helv. **15**, 1507), with CrO_3, β-dihydroxy-carotene, $C_{40}H_{58}O_2$, m.p. 184° (*Kuhn*

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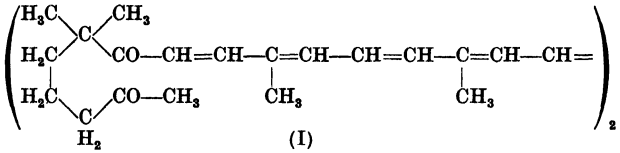
of the goose, and picofulvene (abs. 450, 424), the yellow pigment of some woodpeckers (*Picus*), are products of the metabolism of lutein in the bird organism (*Brockmann* and *Volker*, Z. physiol. Chem. **224**, 193).

[3] Chromatographic analysis of the red pigment gives not only lutein, zeaxanthin and kryptoxanthin, but also the violet red capsorubin (abs. 541, 503, 470 in CS_2), which is also a carotenoid of the C_{40}-series (*Zechmeister* and *Cholnoky*, Ann. **509**, 269).

[4] There are two other carotenoid-carboxylic acids present as pigments in aquatic animals: *asteric acid*, $C_{28}H_{40}O_4$ (abs. 550, 490, 478, 464–450 in dilute acetic acid), from various starfish (echinoderms) such as *Asterias rubens* (v. *Euler* and *Hellström*, Z. physiol. Chem. **223**, 89), and *salmenic acid* (abs. 525, 485) from the salmon (v. *Euler*, *Hellström* and *Malmberg*, C. 1933 II 1037); two other pigments are *glycymerene*, m.p. 148–153° (abs. 495 in CS_2) from *Pectunculus glycymeris*, and the brown-violet *actinio-erythrin* (abs. 574, 533, 495 in CS_2) from *Actina equina* (*Fabre* and *Lederer*, Bull. Soc. Chim. biol. **16** (1934), 105).

The pigments of several bacteria and fungi have also been characterised as carotenoids: *bacteriopurpurin* (abs. 585–555, 540–515, 500–485 in CS_2), see *Molisch*, Die Purpurbakterien (Jena, 1907); *Karrer* and *Solmssen*, Helv. **18**, 1311; **19**, 3, 1019; α- and *β-bacteriorubin* (abs. α-522, 490, 460, β- 502, 482, 452, in alcohol) (*Schneider*, C. 1936 I 3525); the violet pigment of the *Bact. halobium* of fish preserves (*Winterstein*, Z. angew. Chem. **47**, 315); *torulene* (abs. 565, 522, 488 in CS_2) from *Torula rubra* (*Lederer*, C. r. **197**, 1694; *Fink* and *Zenger*, C. 1934 I 3480; II 1218; *Lederer*, C. r. Soc. Biol. **117** (1934) 1083); *coralene* (abs. 509–485, 465–455 in ether) from *Streptothrix corallinus*, and *sarcinene* (abs. 469, 444, 415 in petrol) from *Sarcina lutea*.

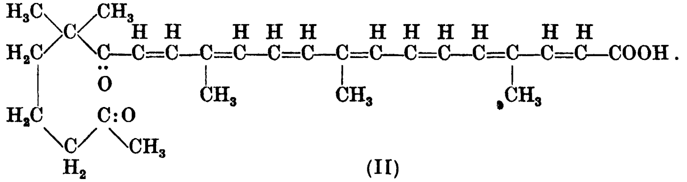
and *Brockmann*, Ber. **67**, 1408; Ann. **516**, 95), neo-β-oxycarotene, m.p. 143°, $C_{40}H_{56}O_2$ (*Karrer* and *Solmssen*, Helv. **18**, 25), and the tetraketone, β-carotenone (I), $C_{40}H_{56}O_4$, m.p. 175° (*dioxime* m.p. 198°) (*Kuhn* and *Brockmann*, Ber. **65**, 894; Z. physiol. Chem. **213**, 1):



(I)

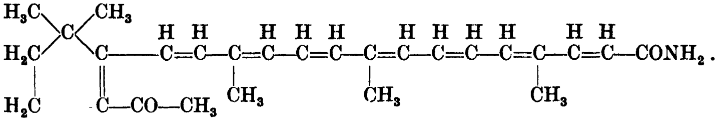
One ring only of β-carotene can be opened by oxidation, giving semi-β-carotenone, m.p. 119° (*monoxime* m.p. 135°), if the oxidation is carried out under carefully regulated experimental conditions (*Kuhn* and *Brockmann*, Ber. **66**, 1319); cf. the analogous oxidation product of α-carotene (*Karrer*, *Solmssen* and *Walker*, Helv. **17**, 417; *Karrer*, *v. Euler* and *Solmssen*, ibid. 1169), and the opening of one ring of zeaxanthin (*Karrer*, *Solmssen* and *Walker*, loc. cit.).

Oxidation by the same method opens the ring of the dihydroxy-monocarboxylic acid, azafrin, to the corresponding diketonic acid, azafrinone (II), $C_{27}H_{36}O_4$, m.p. 191° (*Kuhn* and *Deutsch*, Ber. **66**, 883):



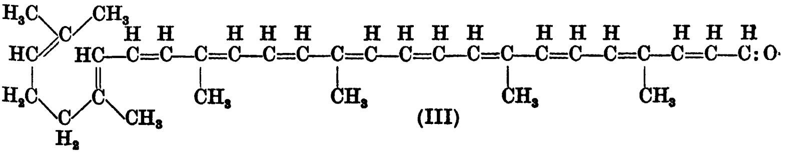
(II)

These oxidation products are 1:6-diketones, and hence can be converted into cyclopentene derivatives, e.g. azafrinone-amide gives dehydro-azafrinone-amide, $C_{27}H_{35}O_2N$, m.p. 210°:

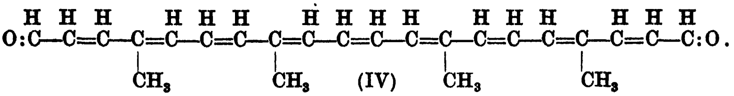


Further treatment with CrO_3 splits out the carbon atoms of the hydroaromatic ring as geronic acid, leaving polyene mono- or dicarboxylic acids (cf. β-carotenone, azafrinone, etc., see *Kuhn* and *Brockmann*, Ber. **67**, 885).

Lycopene can be converted into lycopenal (III), $C_{32}H_{42}O$, m.p. 147° (*oxime* m.p. 198°), and hence into bixin-dialdehyde (IV), $C_{24}H_{28}O_2$, m.p. 220°, by the loss of methyl-heptenone (*p-nitrophenylhydrazone* m.p. 101°) (*Kuhn* and *Grundmann*, Ber. **65**, 898; *Kuhn* and *Roth*, ibid. 1285; *Kuhn* and *Grundmann*, ibid. 1880):



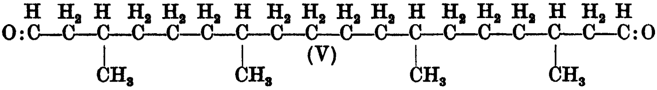
(III)



$O{:}CH{-}CH{=}CH{-}C(CH_3){=}CH{-}CH{=}CH{-}C(CH_3){=}CH{-}CH{=}CH{-}CH{=}C(CH_3){-}CH{=}CH{-}CH{=}C(CH_3){-}CH{=}CH{-}CH{:}O$

(IV)

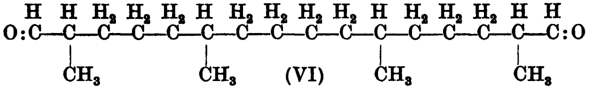
The αα′-dihydroxy-derivative of the saturated dicarboxylic acid corresponding to (IV), which is perhydro-norbixin, $C_{24}H_{46}O_4$, was allowed to react with a Grignard reagent, and the resulting glycol was degraded by the method of *Criegee* to 3:7:12:16-tetramethyloctadecane-1:18-dialdehyde (V), $C_{22}H_{42}O_2$, b.p. 185°/0·3 mm. (*Karrer* and co-workers, Helv. 15, 1399):



$O{:}CH{-}CH_2{-}CH(CH_3){-}CH_2{-}CH_2{-}CH_2{-}CH(CH_3){-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CH(CH_3){-}CH_2{-}CH_2{-}CH_2{-}CH(CH_3){-}CH_2{-}CH{:}O$

(V)

Repetition of the process with the acid formed by mild oxidation of the dialdehyde (V), viz., 3:7:12:16-tetramethyl-octadecane-1:18-dicarboxylic acid, led to 2:6:11:15-tetramethyl-hexadecane-1:16-dialdehyde (VI), $C_{20}H_{38}O_2$ (*Raudnitz* and *Peschel*, Ber. 66, 901):



$O{:}CH{-}CH(CH_3){-}CH_2{-}CH_2{-}CH_2{-}CH(CH_3){-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CH(CH_3){-}CH_2{-}CH_2{-}CH_2{-}CH(CH_3){-}CH{:}O$

(VI)

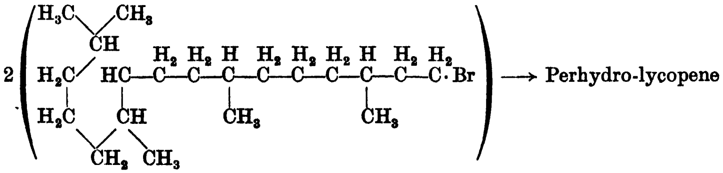
Oxidation of this compound gave the corresponding dicarboxylic acid, perhydro-crocetin, $C_{20}H_{38}O_4$.

The oxidation of bixin with manganic acetate in acetic acid or acetic anhydride is noteworthy, because the molecule is attacked in the middle of the chain; the products are the acetates of hydroxy-compounds,

$$C_{25}H_{30}O_4(OH)_2(O{\cdot}CO{\cdot}CH_3)_2 \text{ and } C_{25}H_{30}O_4(OH)(O{\cdot}CO{\cdot}CH_3)_3.$$

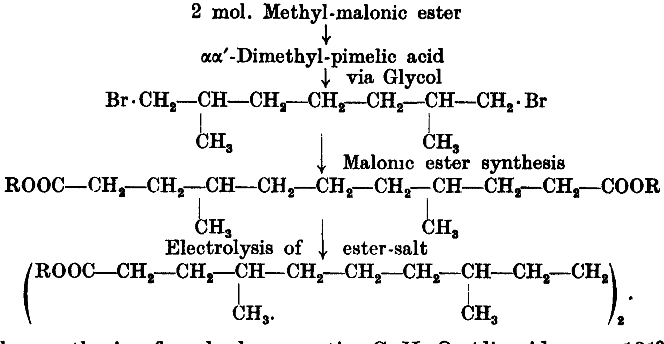
After hydrogenation, they can be oxidised with Pb tetracetate to a pleasant smelling ester-aldehyde, $C_{13}H_{24}O_3$, which is sensitive to air (*Vieböck*, Ber. 67, 377).

The syntheses of the perhydro-compounds of several carotenoids has provided an additional proof of the correctness of the structure which had been allotted to these compounds from the results of the oxidation method. The perhydro-lycopene, $C_{40}H_{82}$, b.p. 240–242°/0·3 mm., prepared from dihydro-phytyl bromide by Wurtz' reaction (*Karrer*, *Helfenstein* and *Widmer*, Helv. 11, 1201; *Karrer*, *Helfenstein*, *Pieper* and *Wettstein*, Helv. 14, 435):



was found to be identical with the hydrogenation product of natural lycopene.

The complete synthesis of perhydro-norbixin, $C_{24}H_{46}O_4$ (*dimethyl ester* b.p. 207°/0·3 mm.; *diamide* m.p. 110·5°), has been carried out in the following stages (*Karrer* and co-workers, Helv. 15, 1218, 1399):



$$\begin{array}{c}
\text{2 mol. Methyl-malonic ester} \\
\downarrow \\
\alpha\alpha'\text{-Dimethyl-pimelic acid} \\
\downarrow \text{ via Glycol} \\
Br\cdot CH_2{-}\underset{\displaystyle CH_3}{\underset{|}{CH}}{-}CH_2{-}CH_2{-}CH_2{-}\underset{\displaystyle CH_3}{\underset{|}{CH}}{-}CH_2\cdot Br \\
\downarrow \text{ Malonic ester synthesis} \\
ROOC{-}CH_2{-}CH_2{-}\underset{\displaystyle CH_3}{\underset{|}{CH}}{-}CH_2{-}CH_2{-}CH_2{-}\underset{\displaystyle CH_3}{\underset{|}{CH}}{-}CH_2{-}CH_2{-}COOR \\
\text{Electrolysis of } \downarrow \text{ ester-salt} \\
\left(ROOC{-}CH_2{-}CH_2{-}\underset{\displaystyle CH_3.}{\underset{|}{CH}}{-}CH_2{-}CH_2{-}CH_2{-}\underset{\displaystyle CH_3}{\underset{|}{CH}}{-}CH_2{-}CH_2\right)_2.
\end{array}$$

The synthesis of perhydro-crocetin, $C_{20}H_{38}O_4$ (diamide m.p. 131°), has been carried out by the same method (*Karrer*, *Benz* and *Stoll*, Helv. **16**, 297).

The partial synthesis of perhydro-norbixin from perhydro-crocetin is described by *Karrer* and *Benz*, Helv. **16**, 337.

Phytol can be converted, via its dihydro-compound, into crocetane (*Willstätter* and *Mayer*, Ber. **41**, 1475, *Fischer*, Ann. **464**, 69; cf. *Karrer* and *Golde*, Helv. **13**, 707).

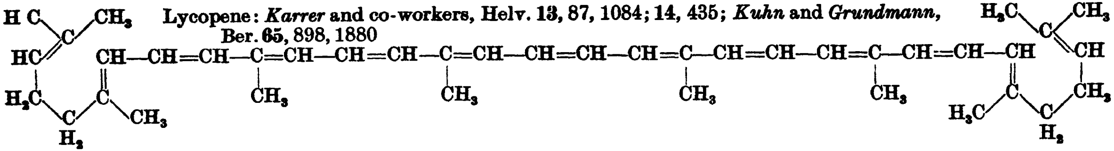
The synthesis of the carbon skeleton of perhydro-vitamin A, $C_{20}H_{40}O$, b.p. 148–150°/0·15 mm., has been achieved from β-ionone, by a series of condensations with bromacetic ester, sodio-malonic ester, CH_3MgI and bromacetic ester (*Karrer*, *Salomon*, *Morf* and *Walker*, Helv. **15**, 878; *Karrer*, *Morf* and *Schopp*, Helv. **16**, 557).

For attempts to synthesise polyene-like compounds, see *Kuhn* and *Hoffer*, Ber. **63**, 2164; **65**, 651; *Fischer* and *Hultzsch*, Ber. **68**, 1726; *Kuhn*, *Badstübner* and *Grundmann*, Ber. **69**, 98; *Kuhn* and *Winterstein*, Helv. **11**, 87; **12**, 493; *Karrer* and *Stoll*, Helv. **14**, 1189; *Fischer* and *Löwenberg*, Ann. **494**, 269; *Postowski* and *Lugowkin*, C. 1933 I 1437; *Gould* and *Thompson*, Am. **57**, 340; *Heilbron*, *Jones*, *Lowe* and *Wright*, J. **1936**, 561; *Salkind*, *Soniss* and *Blochin*, Compt. rend. Acad. Sci. U.R.S.S. **1935** II 57.

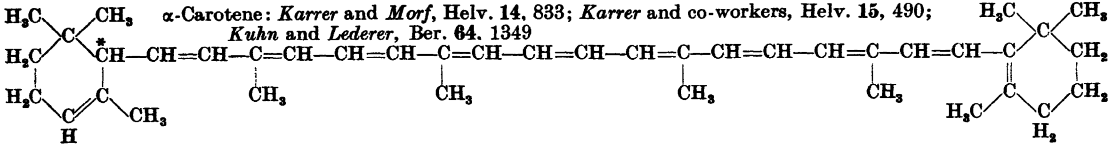
On the basis of the results obtained by the methods which have been described, the structural formulae of the polyene colouring matters may be regarded as established; they are collected together in the following table.

For preliminary formulae for kryptoxanthin, see *Kuhn* and *Grundmann*, Ber. **66**, 1746; for rubixanthin, see idem, Ber. **67**, 339; for xanthophyll (lutein), see *Nilsson* and *Karrer*, Helv. **14**, 843; *Karrer*, *Zubrys* and *Morf*, Helv. **16**, 977; for capsanthin, see *Karrer* and co-workers, Helv. **14**, 625.

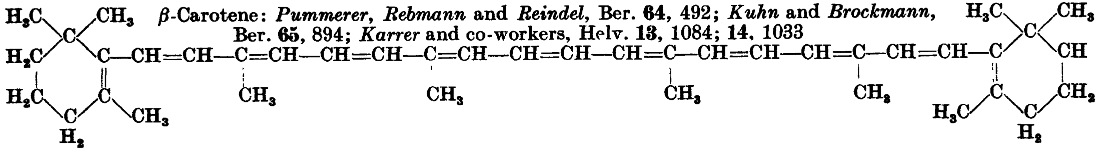
The biochemistry of the carotenoids. For the possibility of phytosynthesis from acetaldehyde, see *Herzig* and *Faltis*, Mo. **35**, 997; the relationship of the carotenoids to isoprene, see *Willstätter* and *Mieg*, Ann. **355**, 19; *Willstätter*, *Mayer* and *Huni*, Ann. **378**, 73; for the possibility that the polyenes are formed from laevulinic acid, see *Emde*, Helv. **14**, 888, and from β-methyl-crotonaldehyde see *v. Euler* and *Klussmann*, C. 1932 II 2201. A biogenetic connection between phytol, or a protophytol, and lycopene and the carotenes



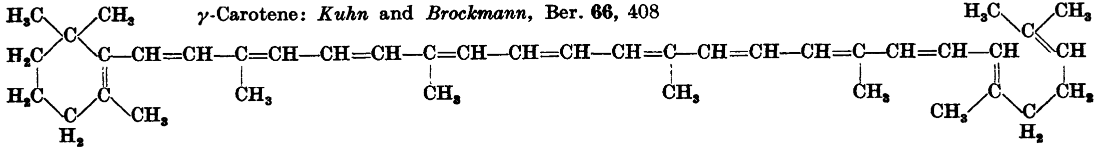
Lycopene: *Karrer* and co-workers, Helv. **13**, 87, 1084; **14**, 435; *Kuhn* and *Grundmann*, Ber. **65**, 898, 1880



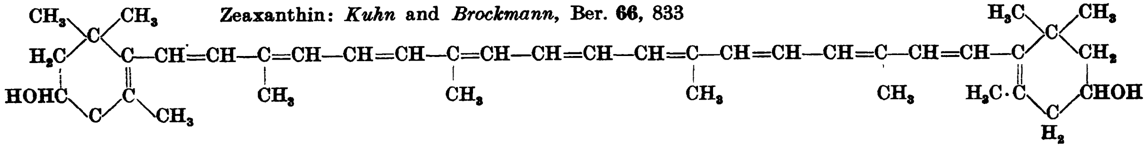
α-Carotene: *Karrer* and *Morf*, Helv. **14**, 833; *Karrer* and co-workers, Helv. **15**, 490; *Kuhn* and *Lederer*, Ber. **64**, 1349



β-Carotene: *Pummerer*, *Rebmann* and *Reindel*, Ber. **64**, 492; *Kuhn* and *Brockmann*, Ber. **65**, 894; *Karrer* and co-workers, Helv. **13**, 1084; **14**, 1033

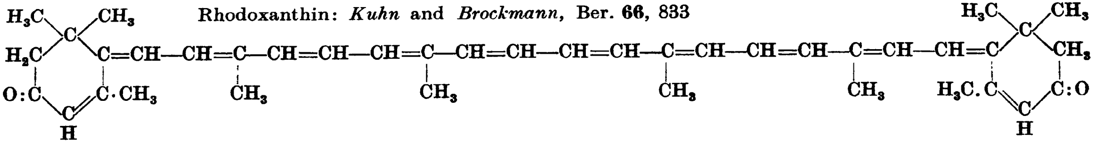


γ-Carotene: *Kuhn* and *Brockmann*, Ber. **66**, 408

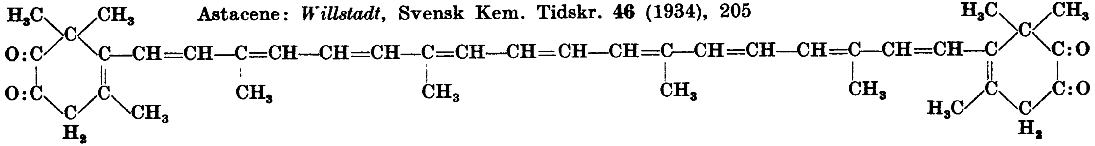


Zeaxanthin: *Kuhn* and *Brockmann*, Ber. **66**, 833

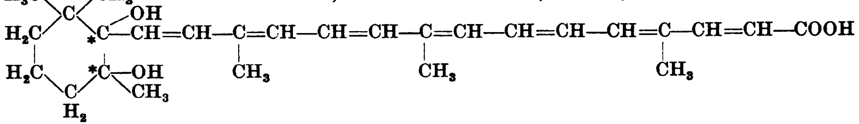
Rhodoxanthin: *Kuhn* and *Brockmann*, Ber. **66**, 833



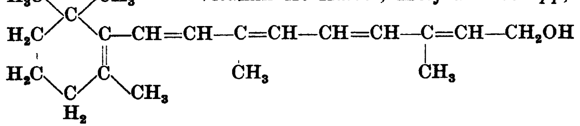
Astacene: *Willstadt*, Svensk Kem. Tidskr. **46** (1934), 205



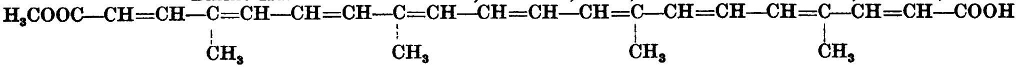
Azafrin: *Kuhn*, *Winterstein* and *Roth*, Ber. **64**, 333; *Kuhn* and *Brockmann*, Ber. **66**, 883



Vitamin A: *Karrer*, *Morf* and *Schöpp*, Helv. **14**, 1431; **16**, 557

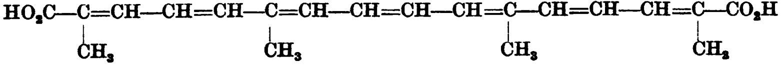


Bixin: *Karrer* and co-workers, Helv. **15**, 1399; *Kuhn* and *Winterstein*, Ber. **65**, 1873



$$H_3COOC-CH=CH-\underset{CH_3}{\underset{|}{C}}=CH-CH=CH-\underset{CH_3}{\underset{|}{C}}=CH-CH=CH-CH=\underset{CH_3}{\underset{|}{C}}-CH=CH-CH=\underset{CH_3}{\underset{|}{C}}-CH=CH-COOH$$

Crocetin: *Karrer* and co-workers, Helv. **15**, 1218, 1399

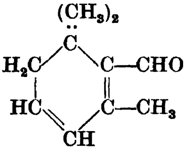


$$HO_2C-\underset{CH_3}{\underset{|}{C}}=CH-CH=CH-\underset{CH_3}{\underset{|}{C}}=CH-CH=CH-CH=\underset{CH_3}{\underset{|}{C}}-CH=CH-CH=\underset{CH_3}{\underset{|}{C}}-CO_2H$$

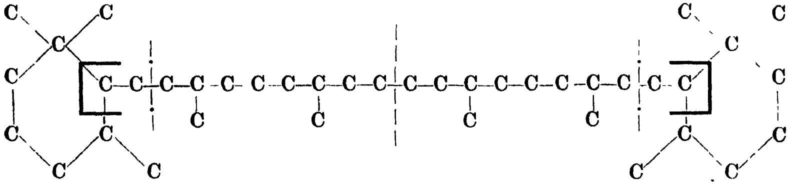
is discussed by *Karrer* and co-workers, Helv. **13**, 1084; *Karrer* and *Helfenstein*, Helv. **14**, 78; *Kuhn* and *Grundmann*, Ber. **65**, 1886.

The fact that zeaxanthin and rhodoxanthin occur together in nature gives considerable support to the supposed genetic connection between the dihydric polyene alcohol zeaxanthin and the corresponding diketone, dihydro-rhodoxanthin (*Kuhn* and *Brockmann*, Ber. **66**, 828).

The products obtained from carotenes by mild oxidation, which have been described above and which are so important for determining the constitution, throw some light on the occurrence in nature of carotenoids containing less than 40 carbon atoms such as astacene, azafrin, asterin- and salmin-carboxylic acids, vitamin A, bixin and crocetin (*Kuhn* and *Winterstein*, Ber. **65**, 646; *Kuhn* and *Brockmann*, ibid. 894; *Kuhn* and *Grundmann*, ibid. 1880; *Kuhn* and *Deutsch*, Ber. **66**, 883; *Kuhn* and *Winterstein*, N. **21**, 527; *Zechmeister* and *v. Cholnoky*, Ann. **509**, 269; *Kuhn*, *Lederer* and *Deutsch*, Z. physiol. Chem. **220**, 229). This view of the origin of many of the lipochromes with shorter chains is further supported by the fact that in some cases the other residues split off from the C_{40}-chain can be found in the same plant; e.g. in the formation of crocetin, $C_{20}H_{24}O_4$, from carotene, $C_{40}H_{56}$, two C_{10}-residues are to be expected; these are met with in the form of an aldehyde, safranal (p. 354), $C_{10}H_{14}O$,



which in combination with glucose can be isolated from the plant (*Crocus sativus*) as picrocrocin (see p. 354) (*Winterstein* and *Teleczky*, Z. physiol. Chem. **120**, 141; Helv. **5**, 376; *Kuhn* and *Winterstein*, Ber. **67**, 344). How various carotenoids may be derived from the chain of 40 carbon atoms is shown in the following formula.



— — — Formation of vitamin A. [ ] Bixin formation
— · — Crocetin formation Azafrin formation

In ripening maize, the disappearance of the free xanthophyll runs parallel with the formation of physalien (*Karrer*, *Helfenstein*, *Wehrli* and *Wettstein*, Helv. **13**, 1084; *Kuhn* and *Brockmann*, Z. physiol. Chem. **206**, 55); in the same way, in the yellowing of the leaves, a very marked esterification of the xanthophyll, lutein and violaxanthin goes hand in hand with the deepening of the colour of the leaves (idem, ibid., 56; *v. Euler*, *Demole*, *Weinhagen* and *Karrer*, Helv. **14**, 831).

Great physiological importance attaches to the growth-promoting activity of carotene (*v. Euler, Karrer* and *Rydbom*, Ber. **62**, 2445; *Kuhn* and *Brockmann*, Ber. **64**, 1859; **66**, 407; *Winterstein*, Z. physiol. Chem. **215**, 51; *Kuhn* and *Brockmann*, N. **21**, 44; *B. v. Euler, H. v. Euler* and *Karrer*, Helv. **12**, 278; *v. Euler, Karrer, Hellström* and *Rydbom*, Helv. **14**, 839), and some of its derivatives, such as dihydrocarotene (idem, ibid.; *Kuhn* and *Brockmann*, Z. physiol. Chem. **213**, 1), diiodo-carotene (*Karrer*, Z. angew. Chem. **42**, 923), monohydroxy-γ-carotene (rubixanthin), β-carotene oxide (*v. Euler, Karrer* and *Walker*, Helv. **15**, 1507), semi-β-carotenone (*Kuhn* and *Brockmann*, Ber. **66**, 1319) and β-hydroxy-carotene (idem, Z. physiol. Chem. **213**, 1; Ber. **65**, 894). This is due to the intermediate formation of vitamin A in the organism, usually in the liver (see *Moore*, Biochem. J. **23** (1929), 802; **24** (1930), 692; *Kuhn* and *Brockmann*, Z. physiol. Chem. **213**, 1; *Kuhn* and *Lederer*, N. **19**, 306; *Kuhn* and *Brockmann*, Ber. **64**, 1859), and therefore indicates the presence of at least one intact β-ionone ring in the molecule of these colouring matters. It is significant that the symmetrical β-carotene is twice as active as the α-compound, since fission of the molecule in the middle can yield two molecules of vitamin A (*Kuhn* and *Brockmann*, Z. physiol. Chem. **213**, 1; **221**, 129; Klin. Woch. **12**, 972). On the other hand, those carotenoids which have no ionone ring (lycopene, bixin, crocetin), or those in which the ionone ring has been opened by oxidation (e.g. the tetraketone, β-carotenone, p. 415), do not behave as a provitamin A. Hydrogenated provitamin A, or carotenes substituted on the ionone ring (e.g. zeaxanthin, rhodoxanthin, astacene, azafrin), are physiologically inactive. In agreement with this, the elimination of the hydroxyl group from zeaxanthin yields a carotenoid with vitamin A properties (*v. Euler, Karrer* and *Zubrys*, Helv. **17**, 24). This biological break-down of the carotenoids is reminiscent of the symmetrical fission of bixin which can be carried out in the laboratory with manganic acetate and lead tetracetate (p. 416).

For the incompatibility of carotene (vitamin A) and thyroxin, see *v. Euler* and *Klussmann*, Z. physiol. Chem. **213**, 21; *Abelin*, ibid. **217**, 109).

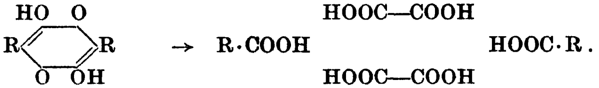
While in the mammalian organism it is predominantly the carotenes (provitamins A) that are absorbed (*Zechmeister* and *Tuzson*, Z. physiol. Chem. **225**, 189), it seems that in birds only the xanthophylls with two OH-groups, such as lutein, zeaxanthin and capsanthin, etc., can be retained in the fat, liver and egg-yolk (*Palmer*, J. Biol. Chem. **23**, 261; **39**, 299; *Zechmeister* and *v. Cholnoky*, Ann. **454**, 54). To some extent, however, a change may take place in these carotenoids; e.g. the xanthophyll of canaries, as is shown by systematic feeding experiments, owes its origin chiefly to a transformation in the bird's organism of the lutein taken in the food (*Brockmann* and *Volker*, Z. physiol. Chem. **224**, 193).

Among the transformations of carotenoids which take place in the animal organism, mention should be made of the hydrolysis of physalien to zeaxanthin in the digestive tract of rats and chickens; another interesting example is the decrease of the ratio of carotene to xanthophyll in the human placenta during the progress of pregnancy (*Kuhn* and *Brockmann*, ibid. **206**, 64).

Experiments on the oxidation of lipoids (unsaturated fatty acids) show that carotenoids belong to the group of compounds which act as catalysts in this oxidation (*Franke*, Ann. **498**, 131; *Ahlström* and *v. Euler*, Z. physiol. Chem. **200**, 233; **204**, 168; *Franke*, ibid. **212**, 234; cf. also *B. v. Euler*, *H. v. Euler* and *Hellström*, Biochem. Z. **203**, 370; *Fodor* and *Frankenthal*, ibid. **246**, 414).

(b) QUINONE COLOURING MATTERS

p-Benzoquinones are met with in nature in various forms. When reduced with Zn dust and acetic anhydride, they give the corresponding hydroquinone acetate, and treatment of dihydroxy-quinones with Na amalgam gives dihydroresorcinols. The constitution of dialkyl-dihydroxy-quinones follows from their ozonolysis products (*Fichter*, *Jetzer* and *Leepin*, Ann. **395**, 8):



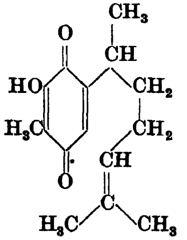
A general method for the synthesis of dialkyl-dihydroxy-quinones consists in condensing oxalic ester with the esters of fatty acids in the presence of metallic Na (*Fichter*, Ann. **361**, 370; *Fichter*, *Jetzer* and *Leepin*, Ann. **395**, 1).

2:6-Dimethoxy-quinone, $C_8H_8O_4$, golden yellow prisms of m.p. 251°, is found in *Herba Adonis vernalis* (*Karrer*, Helv. **13**, 1424). The compound can be synthesised by the energetic oxidation of pyrogallol trimethyl ether, which is the evidence for this formula (*Graebe* and *Hess*, Ann. **340**, 237).

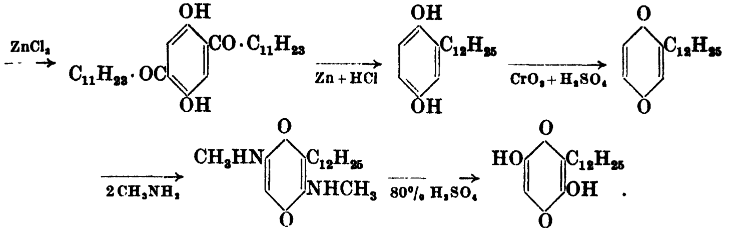
Methoxy-dihydroxy-toluquinone, $C_8H_8O_5$, almost black leaflets of m.p. 203° (diacetate, yellow, m.p. 139·5°), is formed biochemically from glucose by various species of *Penicillium* (*Birkinshaw* and *Raistrick*, Phil. Trans. 1931, B **220**, 1).

Thymoquinone, $C_{10}H_{12}O_2$, yellow plates of m.p. 48°, is present in the essential oil of *Monarda fistulosa* and *Thuja articulata*.

Perezone, *pipitzahoic acid*, $C_{15}H_{20}O_3$, m.p. 104°, $[\alpha]_D$ — 17·0° (ether), is obtained from American pipitzahoac roots from species of *Perezia* (*Radix Pereziae*) and from *Acourtia formosa* (*Mylius*, Ber. **18**, 480; *Fichter*, *Jetzer* and *Leepin*, Ann. **395**, 15). According to the results of *Kögl*, the pigment is methyl-octenyl-hydroxy-benzoquinone (*Kögl* and *Boer*, Rec. **54**, 779; see p. 327):

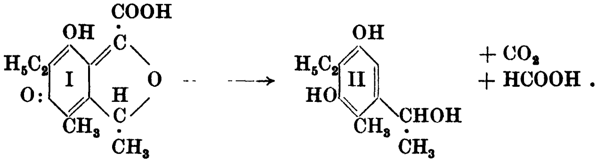


Embelin, $C_{18}H_{28}O_4$, golden plates, m.p. 143° (*dibenzoate* m.p. 98°), is the coloured principle of the fruit of *Ribes embelia*. Oxidation of this dihydroxy-quinone gives lauric acid, m.p. 42°, and hydrolysis with boiling NaOH yields α-keto-myristic acid, $C_{14}H_{26}O_3$ m.p. 63·8°, which can be degraded further with HNO_3 to tridecanoic acid, m.p. 43°. The synthesis of embelin from hydroquinone and lauric acid has been achieved in the following stages (*Hasan* and *Stedman*, J. **1931**, 2112; *Kaul*, *Rây* and *Dutt*, J. Indian Chem. Soc. **8** (1931), 231; *Nargund* and *Bhide*, ibid. 237):

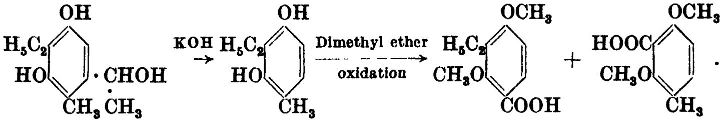


Certain of the natural colouring matters derived from phloroglucinol are closely related to this class of compounds; examples are the **filix tannins** (p. 399), the bitter substance of hops, **humulone** (p. 400), and **usnic acid** of lichens (p. 401), which have been dealt with already in the section on Condensed Tannins.

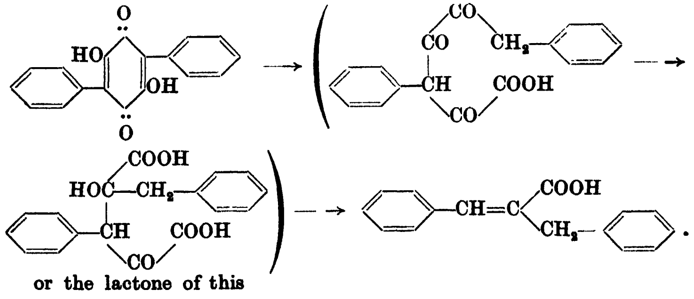
The fungus *Penicillium citrinum* can synthesise from glucose under certain conditions the pigment **citrinin** (I), $C_{13}H_{14}O_5$, m.p. 166–170°, a yellow iso-coumarone derivative (*Hetherington* and *Raistrick*, Phil. Trans. 1931, **B 220,1**):



Its constitution has been established by investigation of the hydrolysis which is shown above. The degradation of the phenolic component (II) is given in the following scheme:



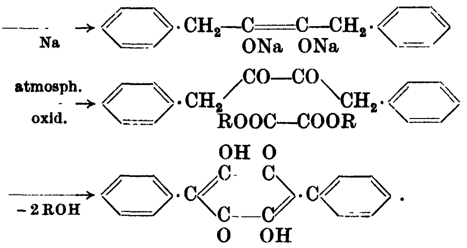
Certain members of the terphenyl-quinone series which occur particularly in fungi will be considered next. That they belong to this group is shown by the fact that they give terphenyl when distilled with Zn dust. The dihydroxy-quinones undergo a characteristic fission with alkali, in which the geometrical isomers of α-benzyl-cinnamic acid are formed by a complicated reaction which seems to involve, first, the opening of the quinone ring, then a benzilic acid rearrangement, and finally oxidation and loss of CO_2:



Their oxidation under certain conditions to derivatives of vulpinic acid (see p. 438), a yellow colouring matter occurring in lichens, is of great biochemical interest (*Kögl* and *Becker*, Ann. **465**, 211).

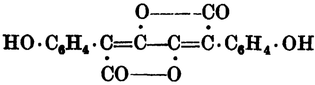
Diphenyl-dihydroxy-quinones can be prepared synthetically by the method of *Fichter* and *Kögl* from phenylacetic ester and oxalic ester, and by *Pummerer's* method, the condensation of quinone with 2 mol. of benzene in the presence of $AlCl_3$ followed by introduction of the hydroxyl groups with alcohol and $ZnCl_2$ (*Kögl*, Ann. **465**, 243; *Pummerer* and *Prell*, Ber. **55**, 3105). Cf. also the partial synthesis of *Adams* (*Shildneck* and *Adams*, Am. **53**, 2373), from p-diaryl-hydroquinones via the p-dibromo-compound to dibromo-diaryl-quinones, which are then hydrolysed to dihydroxy-diaryl-quinones.

Polyporic acid, $C_{18}H_{12}O_4$, is of a brownish yellow colour, and is found in *Polyporus nidulans*, a fungus on oak-trees. Zinc dust distillation of the dihydroxy-quinone gives terphenyl, $C_6H_5{\cdot}C_6H_4{\cdot}C_6H_5$, m.p. 207°. Since oxidation with CrO_3 gives nothing but benzoic acid, both phenolic hydroxyls must be attached to the quinone nucleus. Alkali fission, according to the above scheme, gives the two isomeric benzyl-cinnamic acids, m.ps. 100° and 158°. The synthesis of polyporic acid from phenylacetic ester and oxalic ester has been carried out in the following stages (*Kögl*, Ann. **447**, 78):



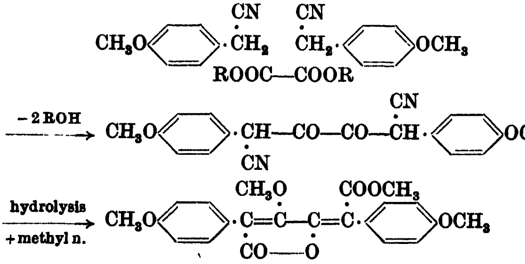
For its preparation from diphenyl-hydroquinone, see *Shildneck* and *Adams*, Am. **53**, 2373.

Atromentin, $C_{18}H_{12}O_6$, the brown colouring matter of the toadstool *Paxillus atrotomentosus*, has been shown by degradation to be p:p′-dihydroxy-polyporic acid (*Kögl*, Ann. **440**, 19; *Kögl* and *Postowsky*, Ann. **445**, 159). Oxidation with H_2O_2 leads to the lactone of atromentic acid,

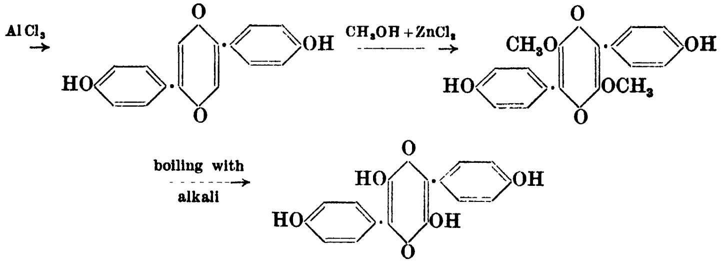


$$\mathrm{HO{\cdot}C_6H_4{\cdot}\underset{CO\text{——}O}{\overset{O\text{——}CO}{C{=}C\text{—}C{=}C}}{\cdot}C_6H_4{\cdot}OH}$$

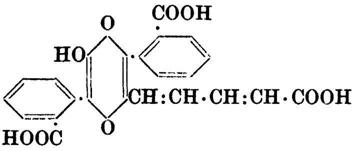
m.p. 346°, which is an analogue of the lactone of vulpinic acid. The constitution of atromentic acid has been confirmed by the following synthesis of its permethylation product:



Atromentin itself has been obtained by the method of *Fichter* and *Kögl* (*Kögl*, Ann. **465**, 243), and also by *Pummerer* from quinone and two mol. of phenol:



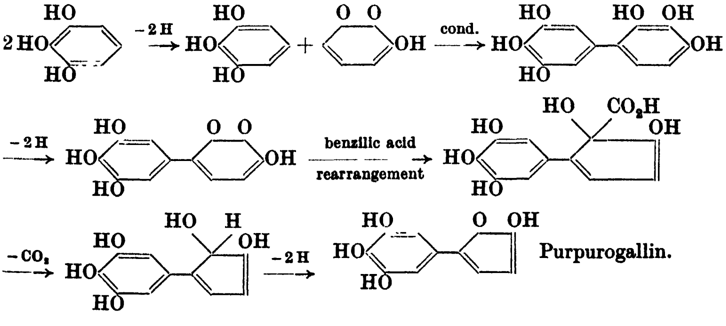
Muscarufin, $C_{25}H_{16}O_9$, m.p. 275·5° (acetate m.p. 197°, orange-yellow), is the red pigment of the fly-agaric, *Amanita muscaria;* it has the constitution



That it is a terphenyl-quinone was determined, as usual, by Zn dust distillation. Catalytic hydrogenation leads to hexahydro-muscarufin, m.p. 200° (triacetate m.p. 192°), which shows the presence of two aliphatic double bonds; these are conjugated, since the compound gives a maleic acid adduct, m.p. 286°. Titration proves the presence of 3 carboxyl groups and their positions are given by the oxidation of hydro-muscarufin with H_2O_2, which yields approximately two molecules of o-phthalic acid, m.p. 203°, and adipic acid, m.p. 151° (*Kogl* and *Erxleben*, Ann. **479**, 11).

The last member of the benzoquinone series to be considered is a derivative of keto-cyclopentadienol; this is **dryophanthin**, $C_{23}H_{28}O_{15}$, dark-red needles of m.p. 220°, which occurs in the red-pea galls of various oaks (*Dryophantha, Quercus*). It is decomposed by heating with dilute sulphuric acid into purpurogallin, $C_{11}H_8O_5$, a dark-red substance of m.p. 275°, and 2 mol. of glucose (*Nierenstein*, J. **115**, 1328).

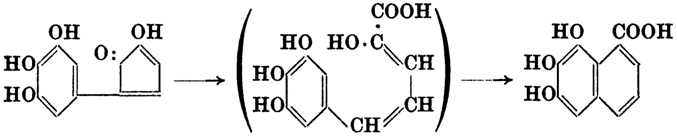
Purpurogallin is probably formed in plants from pyrogallol by the following series of enzymatic reactions (*Willstatter* and *Heiss*, Ann. **438**, 17; *Haber* and *Willstätter*, Ber. **64**, 2844):



Purpurogallin.

For the use of this reaction for the determination of peroxidase, see *Willstätter* and *Stoll*, Ann. **416**, 21. The colouring matter also probably occurs as an intermediate in the formation of humic acid from natural pyrogallol derivatives.

The constitution of purpurogallin is based further upon the existence of a colourless tetracetate, m.p. 180°, tetracetate-phenylhydrazone, m.p. 258°, trimethyl ether, m.p. 177°, and tetramethyl ether, m.p. 94° (*Nierenstein* and *Spiers*, Ber. **46**, 3151). The action of hot alkali brings about a second benzilic acid rearrangement to give purpurogallone, $C_{11}H_8O_5$, m.p. 273°, a trihydroxy-naphthalene-carboxylic acid (*Perkin*, J. **101**, 803):



Similarly, Zn dust distillation yields naphthalene, m.p. 80°, as a result of pyrogenic ring-closure (*Perkin*, Proc. **21**, 211).

Naphthaquinone colouring matters are also found in nature.

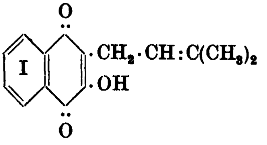
Juglone, $C_{10}H_6O_3$, a yellow-brown substance, m.p. 155°, has been shown by degradation and synthesis to be 5-hydroxy-1:4-naphthaquinone (vol. III). It occurs as a leuco-compound in unripe walnut shells (*Juglans regia*), and was used in the Middle Ages as a brown dyestuff.

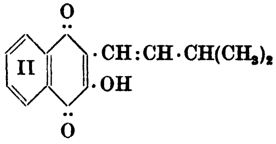
Lawsone, $C_{10}H_6O_3$, m.p. 190° (monoacetate m.p. 129°; dioxime m.p. 200°), the lemon-yellow pigment of the Indian shrub *Lawsonia alba* ("Mehidi"), has been shown to be 2-hydroxy-naphthaquinone, and is isomeric with juglone; Zn dust distillation in a current of hydrogen gives naphthalene, and the action of acetic anhydride and Zn yields a colourless triacetyl-dihydro-compound, m.p. 134·5°. The phenolic hydroxyl is attached to the quinone nucleus, since phthalic acid is obtained on oxidation with $KMnO_4$ (*Lal* and *Dutt*, J. Indian Chem. Soc. **10** (1933), 577). The colouring matter is of biological interest because of its action as a promoter of respiration (*Adler* and *v. Euler*, Z. physiol. Chem. **225**, 41).

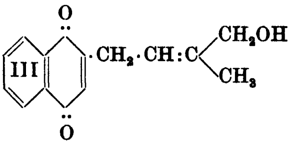
The coloured principle of the bark of the roots of various species of *Plumbago*, previously used in India as a medicine under the name of "chita", is the orange-yellow compound, **plumbagin,** $C_{11}H_8O_3$, m.p. 78° (acetate m.p. 115°). *β*-Methylnaphthalene can be isolated from the Zn dust distillation of the pigment (*Roy* and *Dutt*, J. Indian Chem. Soc. **5** (1928), 419). Observations on its absorption spectrum (*Gomez*, C. 1931 II 819), the existence of quinhydrone compounds (*Madinaveitia* and *de Buruaga*, C. 1930 I 684), and the reduction with Zn and acetic acid to the corresponding colourless hydroquinone, m.p. 86° and 152° (*Madinaveitia* and *Olay*, C. 1933 I 2814), indicate that it is a naphthaquinone derivative (*Madinaveitia* and *Gallego*, C. 1929 I 662; *Katti* and *Patwardhan*, J. Indian Inst. Sci., A, **15**, 9; *Buruaga*, C. 1933 I 3312). Its constitution as 2-methyl-5-hydroxy-1:4-naphthaquinone has been finally proved by its synthesis from m-toluyl chloride and acetylsuccinic ester (*Fieser* and *Dunn*, Am. **58**, 572). Plumbagin is also formed by the oxidation of 2-methyl-1:4-naphthaquinone with Caro's acid (*Buruaga* and *Verdu*, An. Esp. fis. quím. **32** (1934), 830).

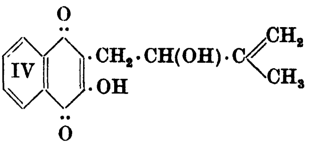
Lapachol (I), $C_{15}H_{14}O_3$, yellow, m.p. 140°, can be isolated from the *Lapacho* tree, a South American member of the family *Bignoniaceae* (*Oesterle*, C. 1912 II 1667; *Matthes* and *Schreiber*, C. 1915 I 162; *Tunmann*, C. 1915 I 399, *Monti*, Gazz. **45** (1915), II, 51). The formation of methyl-naphthalene and isobutylene on Zn dust distillation, the energetic reduction with HI and P to *β*-isoamyl-naphthalene, its oxidation on the one hand to phthalic acid

(*Paternò* and *Caberti*, Gazz. **21** (1891), 374; *Monti* l. c.) and on the other to nor-lapachol, $C_{14}H_{12}O_3$, a red compound m.p. 120° (*Hooker*, Am. **58**, 1168), and a consideration of its absorption spectrum (*Hooker*, Am. **58**, 1163, 1168) have led to the constitutional formula (I) for lapachol. Lapachol has been synthesised from isoprene hydrobromide and β-hydroxy-naphthaquinone (*Fieser*, Am. **49**, 857). Isolapachol (II), a red substance, m.p. 120°, an isomer of lapachol differing in the position of the double bond, has been prepared from 2-hydroxy-1:4-naphthaquinone and isovaleraldehyde (*Hooker* and *Greene*, Ber. **22**, 1723; J. **69**, 1355), and on catalytic reduction gives dihydro-lapachol, a yellow substance m.p. 93·5–94·5° (*Hooker*, Am. **58**, 1163).



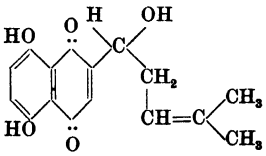






Lomatiol (III), $C_{15}H_{14}O_4$, yellow needles m.p. 127°, from *Lomatia illicifolia* and *longifolia*, is a hydroxy-lapachol (*Rennie*, J. **67**, 787), as is shown by the catalytic hydrogenation to dihydro-lomatiol, yellow needles of m.p. 101–102°, and dihydrolapachol (above) (*Hooker*, Am. **58**, 1181). It undergoes isomeric change (the allyl rearrangement) to isolomatiol (IV), m.p. 110°, which can be converted into lapachol (I) by hydrogenation and dehydration (*Hooker*, J. **69**, 1381).

Alkannin, $C_{16}H_{16}O_5$, a brown-red substance m.p. 149°, $[\alpha]^{20}_{Cd}$ 170° (benzene), was formerly used as a dyestuff for silk and cotton; it is present in the roots of *Alkanna tinctoria* in the form of its red oily angelic ester. Mild hydrolysis of the latter gives the free colouring matter which has the above composition (*Brand* and *Lohmann*, Ber. **68**, 1487). Vacuum sublimation brings about loss of a side-chain, and yields naphthazarin (5:8-dihydroxy-1:4-naphthaquinone). Several views have been held as to the constitution of alkannin, but the evidence now available indicates the following formula (*Brockmann* et al., N. **23**, 246; Ann. **521**, 1; *Brand* and *Lohmann*, l. c.):



Alkannin.

Shikonin, $C_{16}H_{16}O_5$, m.p. 147°, from shikon roots (*Lithospermum erythrorrhizon*), is the optical antimer of alkannin (*Brockmann* and *Roth*, N. **23**, 246).

Colouring matters of the anthraquinone series have been observed both in the plant and in the animal kingdom. Anthraquinone (hoelite) and a derivative of hexahydroxy-anthraquinone (graebite) are found in the mineral kingdom in soft slate (*Treibs* and *Steinmetz*, Ann. **506**, 171).

Anthraquinone pigment	Occurrence	Literature
Alizarin, $C_{14}H_8O_4$ (1:2-dihydroxy-anthraquinone), orange, m.p. 289°	Pentosido-β-glucoside "ruberythric acid" (yellow, m.p. 158–160°) in madder root (*Rubia tinctorum*); 1-monomethyl ether in the Indian chay root (*Oldenlandia umbellata*)	*Baeyer* and *Caro*, Ber. 7, 968; *Gerstl*, Ber. **9**, 281; *Liebermann* and *Bergami*, Ber. **20**, 2241; *Glaser* and *Kahler*, Ber. **60**, 1349; *Schunk*, Ann. **66**, 174; *Jones* and *Robertson*, J. **1933**, 1167
Purpuroxanthin, $C_{14}H_8O_4$ (1:3-dihydroxy-anthraquinone), yellow, m.p. 263°	Madder root	*Liebermann* and *v. Kostanecki*, Ann. **240**, 266
Munjistin, $C_{15}H_8O_6$ (purpuroxanthin-carboxylic acid), yellow-brown, m.p. 231°	Madder root	*Mitter* and *Biswas*, Ber. **65**, 622
Hystazarin, $C_{14}H_8O_4$ (2:3-dihydroxy-anthraquinone)	Monomethyl ether (m.p. 232°) in chay root	see vol. III
Anthragallol, $C_{14}H_8O_5$ (1:2:3-trihydroxy-anthraquinone)	1:2- and 1:3-dimethyl-ethers in chay root	see vol. III
Santalin, $C_{15}H_{14}O_5$ (?) (1:3-dihydroxy-2-methoxy-5:6:7:8-tetrahydro-anthraquinone), red, m.p. 104°	Colouring matter of red sandalwood (*Pterocarpus santalinus*)	*Lehmann*, Z. angew. Chem. **43**, 1119; *Cain*, *Simonsen* and *Smith*, J. **105**, 1335; but see *Raudnitz*, *Navratil* and *Benda*, Ber. **67**, 1036
Purpurin, $C_{14}H_8O_5$ (1:2:4-trihydroxy-anthraquinone), red, m.p. 263°	Madder root	*Dimroth* and *Fick*, Ann. **411**, 315; *Marshall*, J. **1931**, 3206
Pseudo-purpurin $C_{15}H_8O_7$ (purpurin-carboxylic acid), red, m.p. 222°	Madder root	*Liebermann* and *Plath*, Ber. **10**, 1618
Boletol, $C_{15}H_8O_7$ (purpurin-carboxylic acid), blue, m.p. 280° decomp.	In the fungi *Boletus satanas*, *B. luridus* and *badius*	*Kögl* and *Deijs*, Ann. **515**, 23
Tectoquinone, $C_{15}H_{10}O_2$ (2-methyl-anthraquinone), yellow, m.p. 176°	Teak wood	*Kafuku* and *Sebe*, Bull. Chem. Soc. Japan **7** (1932), 114
Rubiadin, $C_{15}H_{10}O_4$ (1:3-dihydroxy-2-methyl-anthraquinone), yellow, m.p. 271°	Glucoside in madder root	*Schunk* and *Marchlewski*, J. **65**, 182; *Jones* and *Robertson*, J. **1930**, 1699

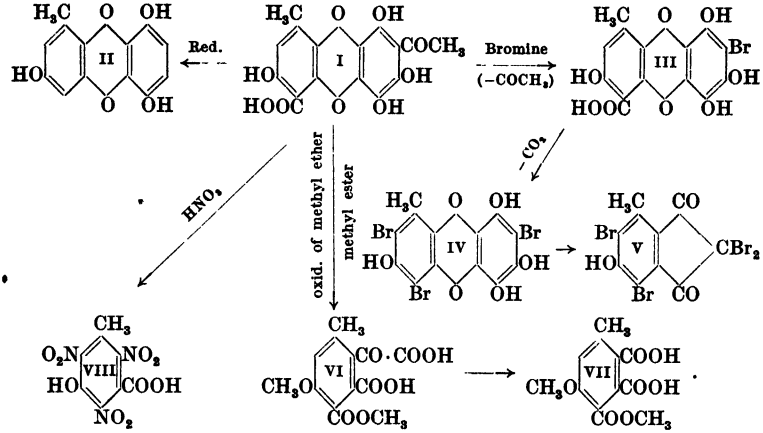
Anthraquinone pigment	Occurrence	Literature
Chrysophanic acid, $C_{15}H_{10}O_4$ (4:5-dihydroxy-2-methylanthraquinone) golden-yellow, m.p. 196°	Glucoside (m.p. 205°) in rhubarb (*Rheum off.*), and in the lichen *Parmelia parietina*	*Hesse*, Ann. **309**, 32; *Fischer* and *Gross*, J. pr. **84**, 372; *Liebermann* and *Fischer*, Ber. **8**, 1104; *Naylor* and *Gardner*, Am. **53**, 4109; *Mohiuddin* and *Katti*, J. Indian Inst. Sci., 1933, A **16**, 1
Aloe-emodin, $C_{15}H_{10}O_5$ (4:5-dihydroxy-2-hydroxymethyl-anthraquinone), orange, m.p. 224°	*d*-Arabinoside (m.p. 147°) in aloe, and senna leaves	*Liebermann*, Ann. **183**, 163; *Léger*, J. Pharm. Chim. (7) **4**, 241; *Seel* and *Kelber*, Ber. **49**, 2364; *Mitter* and *Banerjee*, J. Indian Chem. Soc. **9** (1932), 375
Rhein, $C_{15}H_8O_6$ (4:5-dihydroxy-anthraquinone-2-carboxylic acid), orange-yellow, m.p. 322°	Chinese rhubarb	*Robinson* and *Simonsen*, J. **95**, 1085; *Oesterle*, C. 1912 I 142; *Eder* and *Widmer*, Helv. **5**, 3; *Mitter* and *Banerjee*, J. Indian Chem. Soc. **9** (1932), 375
Emodin, $C_{15}H_{10}O_5$ (4:5:7-trihydroxy-2-methyl-anthraquinone) orange, m.p. 255°	Blood-red agaric (*Dermocybe sanguinea*); rhamnoside "frangulin" (m.p. 286°) in alder-buckthorn (*Rhamnus frangula*); glucoside "polygonin" (m.p. 203°) in *Polygonum cuspidatum*; glucoside of monomethyl ether "rheochrysin" (m.p. 204°) in rhubarb (*Rheum off.*), *Polygonum cusp.*	*Liebermann*, Ann. **183**, 163; *Thorpe* and *Miller*, J. **61**, 1; *Perkin*, J. **67**, 1084; *Kögl* and *Postowsky*, Ann. **444**, 1; *Eder* and *Hauser*, Helv. **8**, 126; *Bridel* and *Charaux*, C. r. **192**, 1269; *Oesterle* and *Johann*, Arch. Pharm. **248** (1910), 476
Endocrocin, $C_{16}H_{10}O_7$ (4:5:7-trihydroxy-2-methyl-anthraquinone-3-carboxylic acid), (emodin-carb. acid), copper-red plates m.p. 318° decomp.	Japanese lichen *Nephromopsis endocrocea*	*Asahina* and *Fuzikawa*, Ber. **68**, 1558
Helminthosporin, $C_{15}H_{10}O_5$ (4:5:8-trihydroxy-2-methyl-anthraquinone), chestnut-brown, m.p. 226°	Metabolism product of the fungus *Helminthosporium gramineum*	*Raistrick*, *Robinson* and *Todd*, J. **1933**, 488; *Charles*, *Raistrick*, *Robinson* and *Todd*, Biochem. J. **27** (1933), 499

Anthraquinone pigment	Occurrence	Literature
Morindone, $C_{15}H_{10}O_5$ (1:5:6-trihydroxy-2-methyl-anthraquinone), orange-red, m.p. 272°	Diglucoside "morindin" (yellow, m.p. 245°) in Indian plant "aal" (*Morinda* species)	*Anderson*, Ann. **71**, 216; *Perkin* and *Hummel*, J. **65**, 851; *Oesterle* and *Tisza*, Arch. Pharm. **245** (1907), 549
Cynodontin, $C_{15}H_{10}O_6$ (1:4:5:8-tetrahydroxy-2-methyl-anthraquinone), bronze plates, m.p. 260°	From the fungus *Helminthosporium cynodontis*	*Raistrick*, *Robinson* and *Todd*, Biochem. J. **27** (1933), 1170
Pentahydroxy-2-methyl-anthraquinone, $C_{15}H_{10}O_7$ m.p. 280°	"Rhodocladonic acid" in lichens of *Cladonia* species	*Hesse*, J. pr. **92**, 449
m.p. 177°	primveroside "rhamnicoside" in buckthorn (*Rhamnus cathartica*)	*Bridel* and *Charaux*, C. r. **180**, 857, 1047; Ann. Chim. (10) **4**, 79
Nataloin, $C_{18}H_{15}O_6\cdot(C_5H_9O_4)$ (3:6-dihydroxy-2-methoxy-methyl-7-ethyl-anthraquinone-3-pentoside), orange	In South African aloe	A. chim. Phys. **6**, 318; **8**, 265; *Seel*, Arch. Pharm. **257** (1919), 212, 229, 254

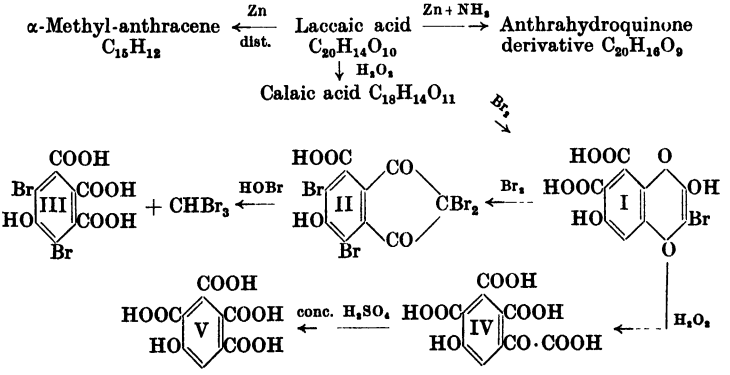
The table given above summarises the constitutions of those members of the group which occur in plants, and gives their occurrence and the more important references to the literature.

The anthraquinone derivatives of animal origin, such as kermessic acid, carminic acid and laccaic acid, have a more complex structure. Their great similarity in absorption spectrum showed that they belong to this group. This was also shown by chemical methods, since distillation with zinc dust gives anthracene and α-methyl-anthracene, and the action of bromine on the cochineal pigment and of oxidising agents gives similar degradation products.

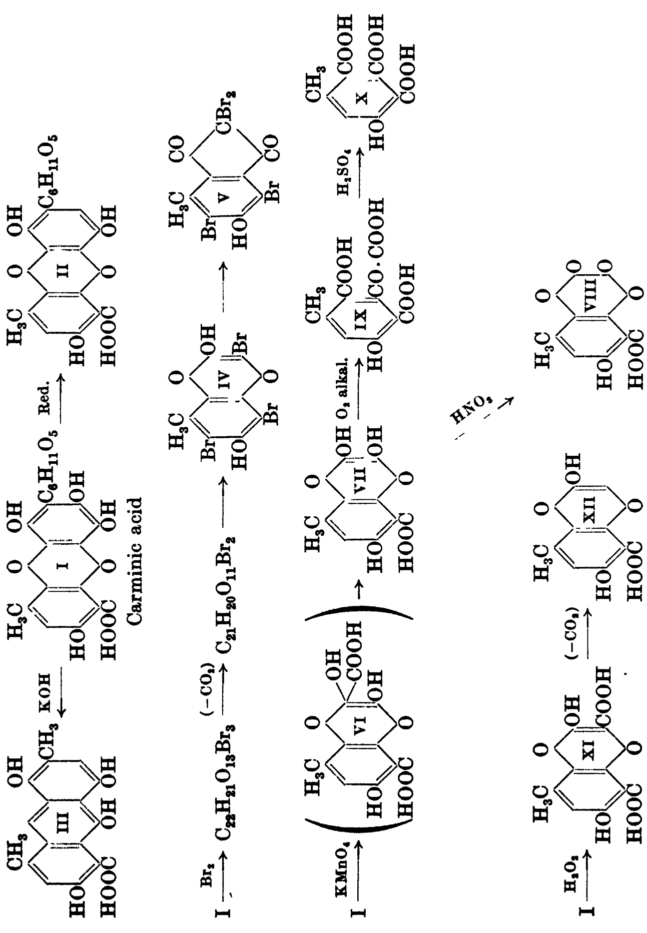
Kermessic acid (I), $C_{18}H_{12}O_9$, decomp. 250°, is the brick-red colouring matter of the insect *Lecanium ilicis*, which is indigenous to the Mediterranean region (*De la Rue*, Ann. **64**, 1; *v. Kostanecki* and *Niementowski*, Ber. **18**, 250). Zinc dust distillation gave anthracene and α-methyl-anthracene, and the structure of the carbon skeleton was also established by reduction of the colouring matter to 3:5:8-trihydroxy-1-methyl-anthracene (II) (*Dimroth* and *Fick*, Ann. **411**, 315; *Dimroth* and *Kammerer*, Ber. **53**, 471). Bromination in acetic acid was accompanied by de-acetylation, giving monobromo-coccin (III), $C_{16}H_9O_8Br$, m.p. 260°; energetic bromination converted this into tribromococcin (IV), $C_{15}H_7O_6Br_3$, m.p. 248°, and finally into α-bromo-carmine (V), $C_{10}H_4O_3Br_4$, an indone derivative (*Dimroth* and *Scheurer*, Ann. **399**, 43). Oxidation of the trimethyl ether of kermessic acid (m.p. 310°) gave the methyl ether methyl ester of cresotin-glyoxyl-dicarboxylic acid (VI), $C_{13}H_{12}O_8$, together with the methyl ether methyl ester of cochinillic acid (VII), $C_{12}H_{12}O_7$ (*Dimroth*, Ber. **43**, 1387). Complete degradation with nitric acid gave nitrococcussic acid (VIII). The following formulae show the relationship of the degradation products to the natural product:



Laccaic acid, $C_{20}H_{14}O_{10}$, the cinnabar-red colouring matter produced by the cochineal insect *Coccus laccae,* was formerly used as a substitute for cochineal under the name "lac dye". The anthraquinone structure of the pigment is established by a comparison of the absorption spectrum and confirmed by distillation with Zn dust. Reduction with Zn and ammonia gives a derivative of anthrahydroquinone, $C_{20}H_{16}O_9$, which is reoxidised by atmospheric oxygen to an anthraquinone derivative, $C_{20}H_{14}O_9$. The oxidation of laccaic acid with H_2O_2 gives calaic acid, $C_{18}H_{14}O_{11}$, which contains three carboxyl groups and one keto group; it is degraded by bromine, via β-bromolaccain (I), $C_{12}H_5O_8Br$, and α-bromolaccain (II), $C_{10}H_2O_5Br_4$, to the substituted aromatic tricarboxylic acid (III), $C_9H_4O_7Br_2$. The naphthaquinone ring of β-bromolaccain is opened by H_2O_2 to yield the α-keto-acid (IV), $C_{11}H_6O_{10}$, which is converted by conc. sulphuric acid into the phenoltetracarboxylic acid (V), $C_{10}H_6O_9$ (*Schmidt,* Ber. **20**, 1285; *Dimroth* and *Goldschmidt,* Ann. **399**, 62; *Tschirch* and *Ludy,* Helv. **6**, 994). In distinction to kermessic acid (see above) and carminic acid, oxidation of laccaic acid with HNO_3 forms picric acid. The following scheme expresses the degradations so far carried out:

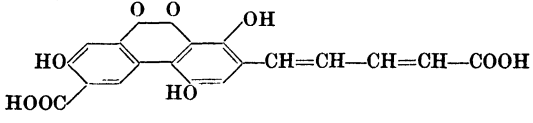


Carminic acid (I), $C_{22}H_{20}O_{13}$, decomp. 136–205°, $[\alpha]_D + 80{\cdot}5°$, is prepared from cochineal, the dried wingless females of the cochineal insect, *Coccus* *cacti coccinelliferi,* which lives on various species of *Cactus* in South and Central America. The red colouring matter, which was used for dyeing wool before the discovery of the azo-dyestuffs, has a close spectroscopic similarity with kermessic and laccaic acids. Zn dust distillation gives a mixture of hydrocarbons, from which anthraquinone and α-methyl-anthraquinone can be obtained by oxidation. Mild reduction eliminates a phenolic hydroxyl group, giving desoxy-carminic acid (II) (see *Dimroth* and *Kammerer,* Ber. **53**, 471). The violent conditions of potash fusion bring about the loss of five carbon atoms of an aliphatic side-chain, with the formation of the anthranol derivative, coccinin (III), $C_{17}H_{14}O_6$, which is readily oxidised by air to coccinone, $C_{17}H_{12}O_7$ (*Hlasiwetz* and *Grabowski,* Ann. **141**, 329; *Dimroth,* Ann. **399**, 1). Careful treatment with bromine yields the bromo-compounds, $C_{22}H_{21}O_{13}Br_3$ and $C_{21}H_{20}O_{11}Br_2$, which are degraded by more energetic bromination into β-bromo-carmine (IV), $C_{11}H_5O_4Br_3$, and then α-bromo-carmine, (V), $C_{10}H_4O_3Br_4$; these reactions involve profound changes in the ring system

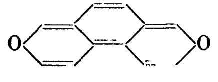


(*Liebermann*, *Höring* and *Wiedermann*, Ber. **38**, 149; *Dimroth*, Ber. **42**, 1611, 1735; *Rohde* and *Dorfmüller*, Ber. **43**, 1363). Carminic acid is oxidised by permanganate, viâ the labile intermediate (VI), into carminazarin (VII), $C_{12}H_8O_7$, decomp. 240–250°, which can be converted on the one hand into the tetraketone carminazarinquinone (VIII), $C_{12}H_6O_7$, and on the other into cochinillic acid (X), $C_{10}H_8O_7$, m.p. 225°, viâ cresotin-glyoxyl-dicarboxylic acid (IX), $C_{11}H_8O_8$, m.p. 230° decomp. Oxidation with H_2O_2 takes a similar course, and the naphthaquinone derivatives (XI) and (XII) are obtained (*Dimroth*, Ann. **399**, 1). Thus the anthraquinone ring of carminic acid carries one methyl group, one carboxyl and four hydroxyl groups; the remainder of the molecule, $C_6H_{11}O_5$, must be an aliphatic chain with four hydroxyl groups which can be acetylated (*Dimroth* and *Kammerer*, Ber. **53**, 471). These various reactions are summarised in the formulae on page 432.

Phenanthraquinone Derivatives. — The red **thelephoric acid,** $C_{20}H_{12}O_9$ (*triacetate*, $C_{26}H_{18}O_{12}$, orange-yellow, decomp. 330°), is obtained from fungi of various species of *Thelephora*. The nine oxygen atoms are present as one quinone group, three phenolic hydroxyl groups and two carboxyl groups because of the formation of pentacetyl-leuco-thelephoric acid and the pentamethyl ether of leuco-thelephoric dimethyl ester, m.p. 246°. It loses two molecules of CO_2 in Zn dust distillation; 2-butadienyl-phenanthrene, $C_{18}H_{14}$, m.p. 125°, is formed, which has been identified by conversion into phenanthrene-2-carboxylic acid, $C_{15}H_{10}O_2$, m.p. 254°, and phenanthrene, $C_{14}H_{10}$, m.p. 97°. When the colouring matter is oxidised with alkaline H_2O_2, hydroxy-trimellitic acid (phenol-2:4:5-tricarboxylic acid), $C_9H_6O_7$, m.p. 241°, can be isolated, which shows that one carboxyl group occupies position 3 in the phenanthrene ring. The position of the second carboxyl group is indicated by the isolation of adipic acid, $C_6H_{10}O_4$, m.p. 150°, from the oxidation products of heptamethyl-hexahydro-thelephoric acid, $C_{27}H_{32}O_9$, m.p. 246°. The rigid proof that the pigment is a 9:10-phenanthraquinone derivative is given by its oxidation by chromic acid to 4:2′:5′-trihydroxy-diphenyl-2:5:4′:6′-tetracarboxylic acid, $C_{16}H_{10}O_{11}$, m.p. 290°; the latter can be decarboxylated to 4:2′:5′-trihydroxy-diphenyl, $C_{12}H_{10}O_3$, m.p. 234°, which is identical with the synthetic product and can be oxidised by H_2O_2 to p-hydroxy-benzoic acid. These various reactions lead to the following constitution for thelephoric acid (*Kögl*, *Erxleben* and *Janecke*, Ann. **482**, 105):



Xylindein, $C_{34}H_{26}O_{11}$, the malachite-green pigment of the fungus *Peziza aeruginosa* which grows on dead beech wood, is also a phenanthrene derivative. Its molecule is derived from the following quinone structure (*Kögl* and *v. Taeuffenbach*, Ann. **445**, 170; *Kögl* and *Erxleben*, Ann. **484**, 65):

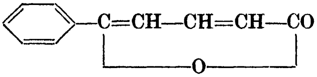


c) COLOURING MATTERS OF THE CUMALIN, CHALKONE AND VULPINIC ACID SERIES

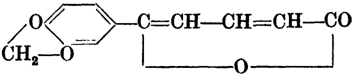
The following section deals with a group of coloured benzene derivatives with unsaturated side-chains, e.g. the colouring matters of coto-bark and kawa root, the curcuma pigment, which is a chalkone, and the vulpinic acid derivatives.

In addition to the benzophenone derivatives described on p. 451, coto-bark contains **phenyl-cumalin** (6-phenyl-α-pyrone), $C_{11}H_8O_2$, a yellowish substance m.p. 68°, and its methylene-dihydroxycompound **paracotoin,** $C_{12}H_8O_4$, a yellow substance m.p. 152°. Potash fusion yields benzoic acid or piperonylic acid, m.p. 228°; the presence of an aromatic nucleus is also shown by nitration of the compounds to $C_{11}H_7O_2(NO_2)$, yellow, m.p. 161°, or to $C_{12}H_6O_4(NO_2)_2$, golden-yellow, m.p. 195°. Degradation with boiling alkali gives acetophenone, C_8H_8O, m.p. 20°, or acetopiperone, $C_9H_8O_3$, m.p. 85°; the same reaction with the methylated compounds, dimethyl-phenyl-cumalin, $C_{13}H_{12}O_2$, m.p. 101°, or dimethyl-paracotoin, $C_{14}H_{12}O_4$, yellow, m.p. 141°, gives phenyl ethyl ketone, $C_9H_{10}O$, b.p. 215°, m.p. 22°, or propiopiperone, $C_{10}H_{10}O_3$, m.p. 38·5°. The olefinic side-chain (2 $\models$), shown to be present by the formation of very unstable hydrobromides and dibromides, is established in phenyl-cumalin by reduction with HI or Na amalgam to phenyl-valeric acid, $C_{11}H_{14}O_2$, m.p. 59°. The existence of the cumalin-ring is proved by the conversion of phenyl-cumalin into α-phenyl-pyridone, $C_{11}H_9ON$, m.p. 197°. The following formulae are therefore assigned to phenyl-cumalin (I) and paracotoin (II) (*Ciamician* and *Silber*, Ber. **27**, 841; *Leben*, Ber. **29**, 1673; *Jobst* and *Hesse*, Ann. **199**, 31):

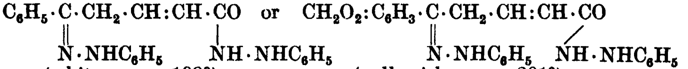
I



II



Phenylhydrazine opens the oxygen ring to give the compounds:



$$\underset{\underset{\textstyle N\cdot NHC_6H_5}{\|}}{C_6H_5\cdot C}\cdot CH_2\cdot CH{:}CH\cdot\underset{\underset{\textstyle NH\cdot NHC_6H_5}{|}}{CO} \quad \text{or} \quad CH_2O_2{:}C_6H_3\cdot\underset{\underset{\textstyle N\cdot NHC_6H_5}{\|}}{C}\cdot CH_2\cdot CH{:}CH\cdot\underset{\underset{\textstyle NH\cdot NHC_6H_5}{/}}{CO}$$

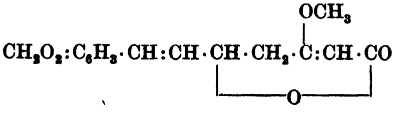
(white, m.p. 198°) (yellowish, m.p. 201°)

The extract of kawa root, *Piper methysticum*, is used in the South Sea Islands for the preparation of the intoxicating national drink, "kawa-kawa"; it contains kawain, yangonin and methysticin, and their dihydro-compounds.

Kawain (I, p. 435), $C_{14}H_{14}O_3$, an almost colourless substance of m.p. 106°, is prepared technically under the name of "gonosan" for the treatment of gonorrhoea. It is converted by caustic soda into kawaic acid (II), $C_{14}H_{14}O_3$, a bright yellow compound of m.p. 186°, and loses CO_2 on distillation to give 6-phenyl-2-methoxy-hexatriene (III), $C_{13}H_{14}O$. Tetrahydro-kawain (V), $C_{14}H_{18}O_3$, m.p. 110°, which can be obtained by the catalytic hydrogenation of kawain, via dihydro-kawain (IV), $C_{14}H_{16}O_3$, m.p. 58°, and also from kawaic acid, similarly loses CO_2 on distillation with the formation of 6-phenyl-2-methoxy-Δ^1-hexene (VI), $C_{13}H_{18}O$, b.p. 138°/16 mm.; mineral acids cause a similar degradation to 6-phenylhexan-2-one (VII), $C_{12}H_{16}O$ (semicarbazone m.p. 141°). The tetrahydro-compound is reduced very slowly to hexahydrokawaic acid (VIII), $C_{14}H_{20}O_3$. A summary of the reactions of kawain is given on p. 435 (*Borsche* and *Roth*, Ber. **54**, 2229; *Borsche* and *Peitsch*, Ber. **62**, 360; **63**, 2414; *Borsche* and *Blount*, ibid. 2418).

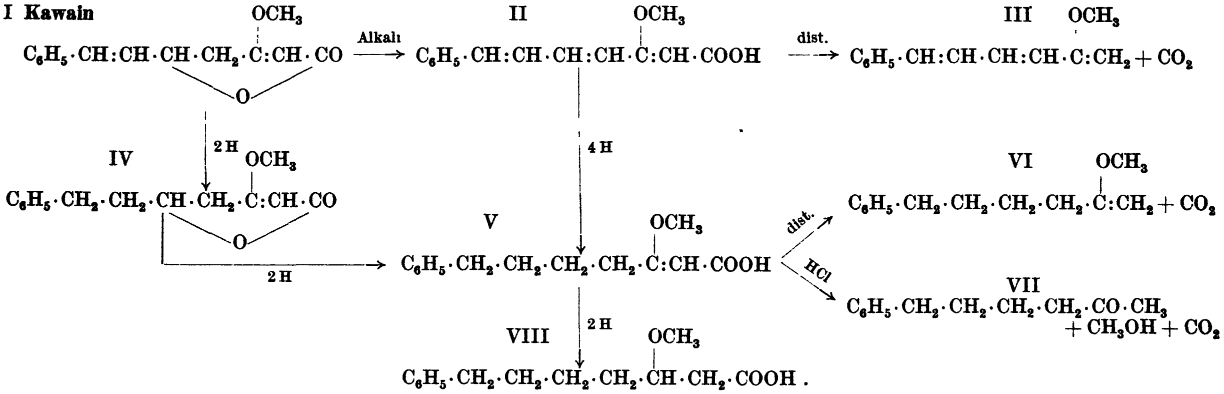
allo-**Kawain,** $C_6H_5\cdot CH{:}CH\cdot CH{:}CH\cdot CO\cdot CH_2\cdot COOCH_3$, m.p. 92°, obtained by demethylation of kawaic acid and esterification by means of the tetramethyl ester of orthosilicic acid, has been synthesised from 4-phenylbutadiene-1-carboxylic acid chloride and the methyl ester of acetoacetic acid (*Borsche*, Ber. **60**, 982; *Borsche*, *Rosenthal* and *Meyer*, ibid. 1135).

Methysticin, $C_{15}H_{14}O_5$, a brown compound m.p. 137°, has been identified by methods similar to those used for kawain, as methylene-dihydroxykawain:

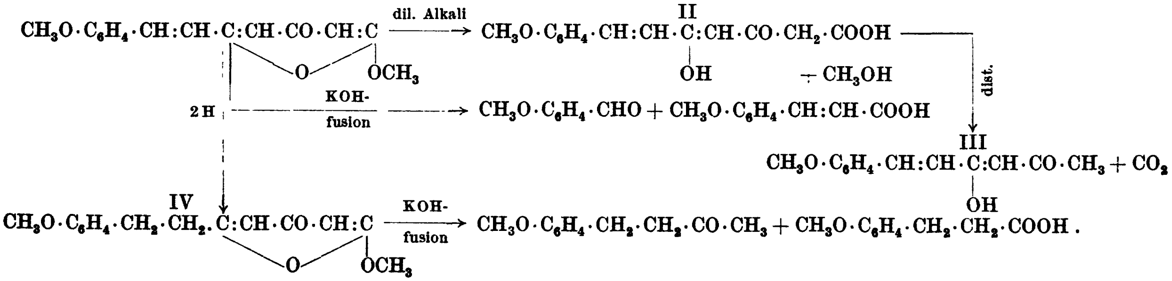


$$CH_2O_2{:}C_6H_3\cdot CH{:}CH\cdot CH\cdot CH_2\cdot\underbrace{\overset{\overset{\textstyle OCH_3}{|}}{C}{:}CH\cdot CO}_{O}$$

I Kawain


II
III
IV
V
VI
VII
VIII
OCH₃
Alkali
dist.
2 H
4 H
2 H
2 H
dist.
HCl
C₆H₅·CH:CH·CH·CH₂·C:CH·CO
O
C₆H₅·CH:CH·CH:CH·C:CH·COOH
C₆H₅·CH:CH·CH:CH·C:CH₂ + CO₂
C₆H₅·CH₂·CH₂·CH·CH₂·C:CH·CO
C₆H₅·CH₂·CH₂·CH₂·CH₂·C:CH·COOH
C₆H₅·CH₂·CH₂·CH₂·CH₂·C:CH₂ + CO₂
C₆H₅·CH₂·CH₂·CH₂·CH₂·CO·CH₃ + CH₃OH + CO₂
C₆H₅·CH₂·CH₂·CH₂·CH₂·CH·CH₂·COOH .

I Yangonin

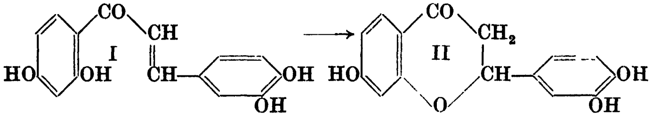

II
III
IV
dil. Alkali
dist.
2 H
KOH-fusion
KOH-fusion
CH₃O·C₆H₄·CH:CH·C:CH·CO·CH:C
O
OCH₃
CH₃O·C₆H₄·CH:CH·C:CH·CO·CH₂·COOH
OH
− CH₃OH
CH₃O·C₆H₄·CHO + CH₃O·C₆H₄·CH:CH·COOH
CH₃O·C₆H₄·CH:CH·C:CH·CO·CH₃ + CO₂
CH₃O·C₆H₄·CH₂·CH₂.C:CH·CO·CH:C
CH₃O·C₆H₄·CH₂·CH₂·CO·CH₃ + CH₃O·C₆H₄·CH₂·CH₂·COOH .

(*Pomeranz*, Mo. **9**, 863; *Borsche*, Ber. **60**, 982; *Borsche, Meyer* and *Peitzsch*, ibid. 2113; 2116; *Borsche* and *Peitzsch*, Ber. **62**, 360; *Borsche* and *Blount*, Ber. **68**, 2418).

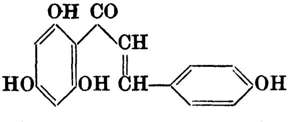
Yangonin (I, p. 435), $C_{15}H_{14}O_4$, a yellow substance m.p. 154°, is hydrolysed by dilute alkali and the γ-pyrone ring also opens to give yangonic acid (II), $C_{14}H_{14}O_5$, a bright-yellow compound m.p. 124°, which loses CO_2 on heating to give yangonol (III), $C_{13}H_{14}O_3$; fusion with alkali destroys the pyrone ring, yielding anisaldehyde (p-methoxy-benzaldehyde) and p-methoxy-cinnamic acid. Catalytic hydrogenation first reduces the double bond between the aromatic nucleus and the pyrone ring, as with kawain, giving dihydroyangonin (IV), $C_{15}H_{16}O_4$; potash fusion of this gives 4-p-methoxy-phenylbutan-2-one and p-methoxy-hydrocinnamic acid (*Borsche* and *Gerhardt*, Ber. **47**, 2902). Those reactions of yangonin which are of importance for determining its structure are shown on p. 435 (*Borsche* and *Bodenstein*, Ber. **62**, 2515; *Borsche* and *Blount*, Ber. **65**, 820).

The **chalkones** are closely related to the flavanones (see p. 360).

The glucoside of **butein** (I), $C_{15}H_{12}O_5$, an orange-red compound of m.p. 214°, identical with the dyestuff "tesu", occurs in the flowers of *Butea frondosa*. It readily undergoes rearrangement into the corresponding flavanone derivative **butin** (II), m.p. 224° (*A. G. Perkin*, Proc. **19**, 134; **20**, 11):

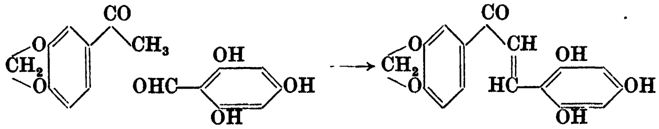


An isomer of butein-glucoside is also known; it is **salipurposide**, $C_{21}H_{22}O_{10}$, the orange-red dyestuff of obtained from various species of *Salix*. Its aglucone, salipurpol, $C_{15}H_{12}O_5$, yields phloroglucinol, $C_6H_6O_3$, m.p. 222°, and p-coumaric acid, $C_9H_8O_3$, m.p. 226°, on fusion with alkali, and hence is dehydrophloretin:

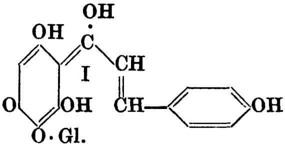


Like phlorrhizin, it produces strong glucosuria (*Charaux* and *Rabate*, Bull. Soc. Chim. Biol. **13** (1931), 814).

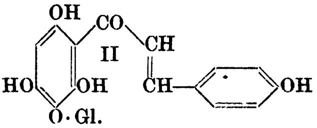
Hyssopin, $C_{16}H_{12}O_6$, an orange substance, decomp. 265–270°, the yellow dyestuff of *Herba hyssopi*, is the rhamnoside of 2:4:6-trihydroxy-styryl-3:4-methylene-dihydroxy-phenyl-ketone (*Oesterle*, Schweiz. Apoth.-Ztg. **59** (1921), 548; **60** (1922), 441). The constitution of this chalkone follows from the products obtained by the action of alkalis, phloroglucinol and piperonal or acetopiperone, and from its synthesis from phloroglucinaldehyde and acetopiperone (*Shriner* and *Kleiderer*, Am. **51**, 1267):



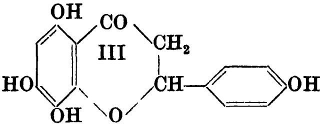
Carthamin (I), $C_{21}H_{22}O_{11}$, m.p. 230°, the red colouring matter of the wild saffron, *Carthamus tinctorius*, is obtained by extracting the leaves with pyridine; isocarthamin (II), $C_{21}H_{22}O_{11}\cdot 2H_2O$, yellow needles of m.p. 228°, can be obtained from the plant by using water and HCl. Fusion with potash gives p-hydroxy-benzoic acid (*Malin*, Ann. **136**, 117), while with dilute alkali p-coumaric acid and p-hydroxy-benzaldehyde are formed (*Kametaka* and *Perkin*, J. **97**, 1415); the potash fusion of dihydro-carthamin, obtained by catalytic reduction, yields p-hydroxy-hydrocinnamic acid and a phenol which not been investigated further. If the glucose is removed from carthamin by hydrolysis with hot dilute H_3PO_4, carthamidin (III), $C_{15}H_{12}O_6\cdot H_2O$, a pale-yellow substance m.p. 218°, is obtained and this has been synthesised from 2-hydroxy-3:4:6-trimethoxy-acetophenone and anisaldehyde (*Bargellini* and *Zoras*, Gazz. **64**, 202); similarly, isocarthamin gives isocarthamidin, $C_{15}H_{12}O_6$, a yellow compound m.p. 240° (*Kuroda*, Proc. Imp. Acad. Tokyo **5** (1929), 32; J. **1930**, 752):



I



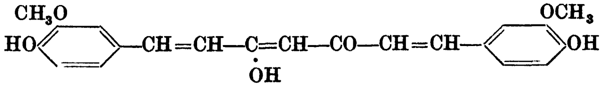
II



III

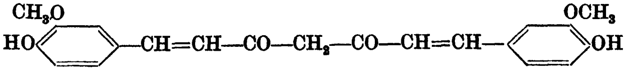
The synthesis of carthamin pentamethyl ether, m.p. 112°, from 1:2:3:5-tetramethoxy-benzene, acetyl chloride and p-methoxy-benzaldehyde proved its constitution as 2:3:4:6:4′-pentamethoxychalkone (*Kuroda*, Proc. Imp. Acad. Tokyo **5** (1929), 86).

Curcumin, $C_{21}H_{20}O_6$, orange-yellow prisms of m.p. 183°, was isolated by *Vogel* and *Pelletier* in 1815 from the roots of *Curcuma longa* and *viridiflora*; it has also been found in rhubarb (*Linde*, Apoth.-Ztg. **31** (1916), 614). The colouring matter dissolves in alkali to give brownish-red salts, and gives an intense ferric chloride reaction; hence it must be an enol. The presence of two phenolic hydroxyl groups is shown by the formation of a dimethyl ether, m.p. 137°, a diacetyl compound, m.p. 171°, and a dicarbethoxy-compound, m.p. 152°; two methoxyl groups are also present. With hydroxylamine, curcumin gives an oxime, $C_{21}H_{21}O_6N$, m.p. 162°, and an isoxazole derivative, $C_{21}H_{19}O_5N$, m.p. 173°; the formation of the latter shows the presence of a 1:3-diketo-group. Catalytic hydrogenation saturates two double bonds and gives colourless tetrahydro-curcumin, $C_{21}H_{24}O_6$, m.p. 96° (*Ciamician* and *Silber*, Ber. **30**, 192). Degradation of curcumin with hot alkali yields vanillic acid, $C_8H_8O_4$, m.p. 207°, and ferulic acid, $C_{10}H_{10}O_4$, m.p. 169° (*Milobedzka*, *v. Kostanecki* and *Lampe*, Ber. **43**, 2163). These experimental results shown that curcumin and is the enol-form of diferuloyl-methane:



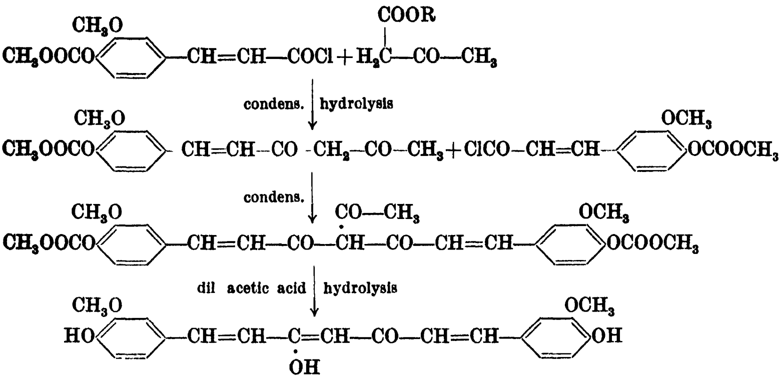
$$HO(CH_3O)C_6H_3{-}CH{=}CH{-}\underset{OH}{C}{=}CH{-}CO{-}CH{=}CH{-}C_6H_3(OCH_3)OH$$

Acetylation in pyridine converts curcumin into the diacetate of isocurcumin, m.p. 154°; the latter is the keto-form (*Ghosh*, J. **115**, 292):



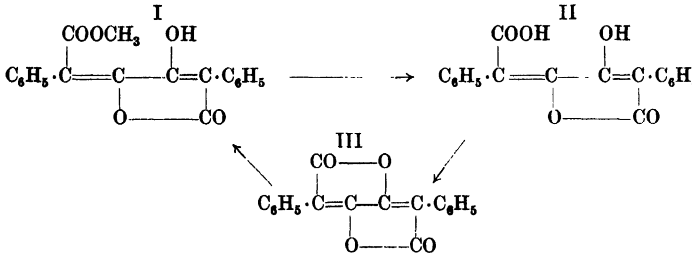
$$HO(CH_3O)C_6H_3{-}CH{=}CH{-}CO{-}CH_2{-}CO{-}CH{=}CH{-}C_6H_3(OCH_3)OH$$

The synthesis of curcumin from two molecules of vanillin and one of acetylacetone does not go smoothly (*Heller*, Ber. **47**, 887, 2998), but it can be obtained from carbomethoxy-feruloyl chloride and acetoacetic ester by the following steps (*Lampe*, Ber. **51**, 1347):

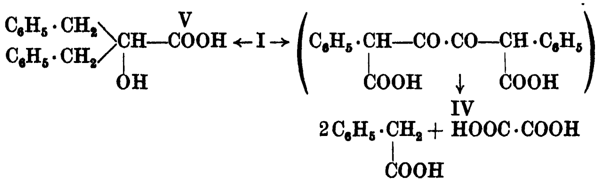


The **vulpinic acid group** contains several deeply coloured lichen colouring matters. They are related biogenetically to the terphenylquinone pigments of the fungi (p. 424).

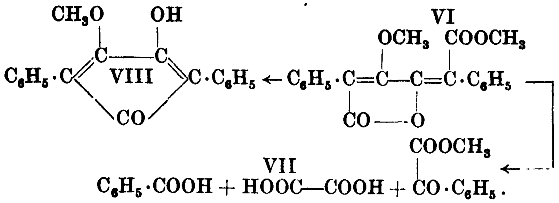
Vulpinic acid (I), $C_{19}H_{14}O_5$, a yellow substance of m.p. 148°, the colouring matter of the lichens *Evernia vulpina*, *Cetraria vulpina* etc., is the methyl ester of pulvinic acid (II), $C_{18}H_{12}O_5$, a brown compound m.p. 216°; with methyl alcohol the latter yields the dilactone (III), $C_{18}H_{10}O_4$, a yellow compound m.p. 221°, and then vulpinic acid again (*Volhard*, Ann. **282**, 1; *Wolff*, Ann. **288**, 14):



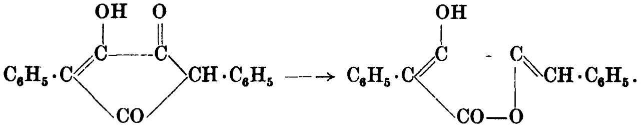
Boiling baryta converts vulpinic acid into 1:4-diphenyl-2:3-diketo-butane 1:4-dicarboxylic acid (diphenyl-ketipinic acid) and then into two molecules of phenylacetic acid and one of oxalic acid (IV) (*Spiegel*, Ann. **299**, 1). Alkalies bring about a benzilic acid rearrangement with loss of two molecules of CO_2 to dibenzyl-glycollic acid (V):



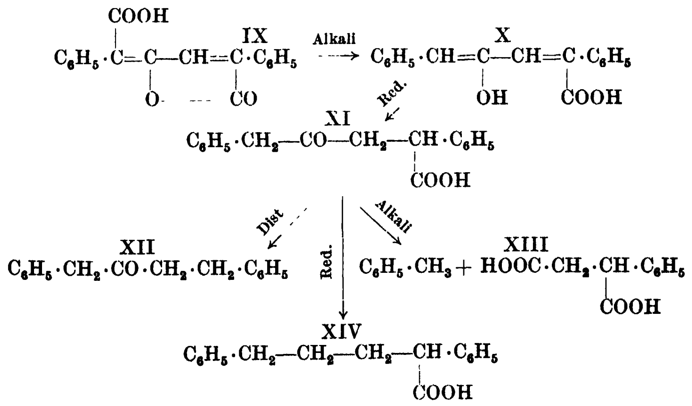
Oxidation of the methyl ether of vulpinic acid (VI) leads to phenyl-glyoxylic ester, oxalic acid and benzoic acid (VII) (*Karrer, Gehrckens* and *Heuss*, Helv. **9**, 446):



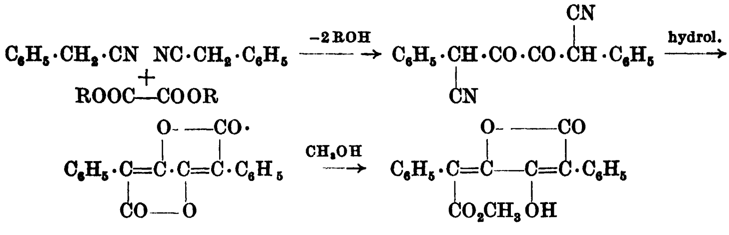
The hydrolysis of the methyl ether with methyl alcoholic potash is a very characteristic reaction: the solution which is originally yellow becomes deep violet after a short time; this is due to hydroxy-quinone ring-closure, and addition of acids precipitates a yellow substance, 2:5-diphenyl-3-hydroxy-4-methoxy-cyclopentadienone (VIII), $C_{20}H_{18}O_5$ (*Kogl*, Ann. **465**, 248). This is the reverse of a rearrangement, observed much earlier (*Claisen* and *Ewan*, Ann. **284**, 250), of oxalyl-dibenzylketone, when it is heated above its m.p. into iso-oxalyl-dibenzylketone ("pulvinone") (p. 60):



The carboxy-cornicularic lactone (IX), $C_{18}H_{12}O_4$, m.p. 215°, obtained from vulpinic acid by reduction, is converted by alkali into cornicularic acid (X), $C_{17}H_{14}O_3$, m.p. 123°, the lactone ring being opened and CO_2 lost; the action of Zn and alkali gives dihydro-cornicularic acid (XI), m.p. 134°, which loses its second carboxyl group on distillation with lime, with the formation of benzyl-phenylethyl ketone (XII). and is hydrolysed by potash to phenyl-succinic acid, $C_{10}H_{16}O_4$, m.p. 167°, and toluene (XIII). Further reduction of dihydro-cornicularic acid with HI and P leads to 1:4-diphenyl-butane-1-carboxylic acid (XIV) (*Thiele*, Ann. **306**, 147; *Thiele* and *Straus*, Ann. **319**, 211):

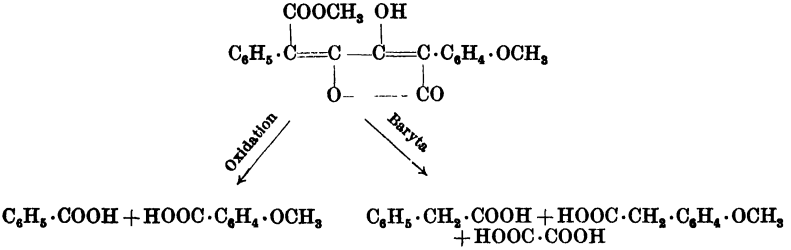


The constitution of vulpinic acid deduced from these degradations is confirmed by its synthesis from benzyl cyanide and oxalic ester (*Volhard*, Ann. **282**, 1; cf. *Kögl*, Ann. **465**, 246):



Dipulvinic acid, $C_{36}H_{22}O_9$, brick-red needles of m.p. 211°, which occurs in the lichen *Candelaria concolor*, is converted by methyl alcohol into two molecules of vulpinic acid, $C_{19}H_{14}O_5$, m.p. 148°, and by acetic anhydride into pulvinic anhydride, $C_{18}H_{10}O_4$, m.p. 220° (*Hesse*, Ber. **30**, 1983).

Lichens of the genus *Cetraria* yield the orange-yellow **pinastric acid,** $C_{20}H_{16}O_6$, m.p. 203° (methyl ether m.p. 153°), a p-methoxy-vulpinic acid, as is shown by its oxidation to anisic acid and benzoic acid, and by its alkali fission to p-methoxy-phenylacetic acid, m.p. 87°, phenylacetic acid and oxalic acid (*Koller* and *Pfeiffer*, Mo. **62**, 160):



This lichen acid has been synthesised by *Asano* and *Kameda* (Ber. **67**, 1522) and by *Koller* and *Klein* (Mo. **63**, 213).

d) FLAVONES, FLAVONOLS, AND ANTHOCYANINS

The majority of the flavones and flavonols are compounds of a yellow colour, but they also occur as colourless glycosides in the corollas of several white flowers (*Nakaoki*, J. Pharm. Soc. Japan **52** (1932), 195, 198). The colours of the anthocyanins depend in the first instance upon the hydrogen ion concentration of the cell sap (*Karrer* and co-workers, Helv. **10**, 742; *Buxton* and *Darbishire*, J. Genetics **21** (1929), 71). Their oxonium salts usually have a red colour, while their alkali salts are blue to violet. The colour is further a function of the number of hydroxyl or methoxyl groups present in the aglycone, and depends also on the nature of the sugar and the acid components. In addition to these factors the presence of specific substances called co-pigments is of importance: examples of such substances are tannin, free acids (e.g. gallic acid, caffeic acid, acetic acid, see *Karrer* and *Schwarz*, Helv. **11**, 916), 2-hydroxy-xanthone and ferric salts (*Willstätter* and *Zollinger*, Ann. **412**, 195; *G. Robinson* and *R. Robinson*, Biochem. J. **25** (1931), 1687), and papaverine hydrochloride (idem, ibid. **28** (1934), 1712); the presence of colloidal matter also has a considerable influence on the colour (see *Robinson*, Brit. Assoc. Rep. **1933**, 53). To some extent the anthocyanins are present in plants as leuco-anthocyanins, which are compounds in the same stage of oxidation; these yield the anthocyanidin chloride with strong HCl without absorption of oxygen (*G. Robinson* and *R. Robinson*, Biochem. J. **27** (1933), 206; *G. Robinson*, J. **1937**, 1157).

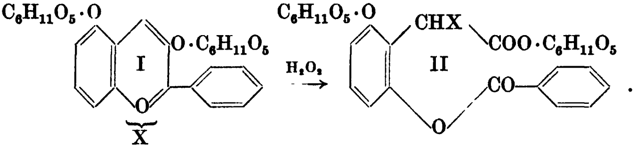
The pigments may be prepared pure through their difficultly soluble salts (chlorides, picrates or heavy metal salts), and by chromatographic analysis (*Karrer*, *Strong* and *Weber*, Helv. **19**, 25, 1025).

Useful summaries of the methods of synthesis which are available in this group will be found in an article by *G. Robinson* and *R. Robinson* (Nature **128** (1931), 413) and a lecture by *R. Robinson* (Ber. **67** (A), 85).

Two reactions have been usefully employed to determine the position of the sugar residue in the anthocyanin.

1. Anthocyanins with a free hydroxyl-group in the 3-position are rapidly decolourised by ferric chloride solution (*Robinson* and coworkers, J. **1931**, 2672), while its substitution stabilises the molecule (*Karrer* and co-workers, Helv. **10**, 729). The same holds for sensitivity to alkali and ease of reduction (idem, ibid., 743).

2. The heterocyclic ring of the anthocyanins (I) can be opened by H_2O_2 in the following way:



If the 3-hydroxyl is carrying a sugar residue, the corresponding sugar-ester (II) is formed, and this is easily hydrolysed by dilute ammonia; a sugar residue attached to the aromatic nucleus, e.g. in the 5-position, is only removed by heating with dilute HCl (*Karrer* and *de Meuron*, Helv. **15**, 507, 1212; *Robinson*, N. **20**, 612).

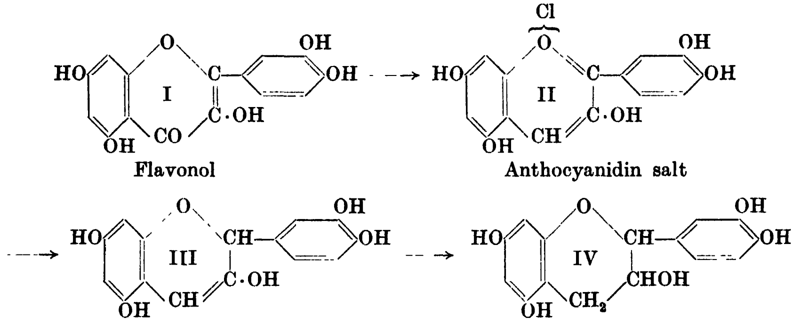
The conclusions drawn from the behaviour towards ferric chloride and from the degradation with H_2O_2 with subsequent hydrolysis are completely confirmed by the synthesis of the anthocyanins themselves which has been carried out by the general method of synthesis of flavylium compounds (see vol. IV) (*Robinson* and coworkers, J. **1928**, 1455, 1460; *Levy*, *Posternak* and *Robinson*, J. **1931**, 2701; *Robinson* and co-workers, ibid. 2665, 2672, 2701; *Leon* and *Robinson*, ibid. 2732; **1932**, 2221; *Robinson* and *Todd*, ibid. 2299, 2488).

The following reactions serve for the rapid characterisation of the anthocyanins or anthocyanidins (*Levy* and *Robinson*, J. **1931**, 2715; *G. Robinson* and *R. Robinson*, Biochem. J. **25** (1931), 1687; **26** (1932), 1647; *Karrer* and co-workers, Helv. **10**, 742):

(I) Change of colour with sodium hydroxide and carbonate.
(II) Typical colourations with ferric chloride in amyl alcohol.
(III) Solubility in cyclohexanol + toluene (1:5).
(IV) Stability towards atmospheric oxygen.
(V) Behaviour towards picric acid in amyl ethyl ether + anisole (1:4).

For the spectroscopic investigation of flavones, etc., see *Robertson* and *Robinson*, Biochem. J. **23** (1929), 35; *Hattori*, Acta phytochim. **5** (1931), 219; **6** (1932), 131; *Schou*, Helv. **10**, 907.

Biogenetic relationships. — Flavones and flavonols (I) can be reduced to anthocyanidins (II) with Na-amalgam (*Asahina*, *Nakagome* and *Inubuse*, Ber. **62**, 3016; *Kondo*, J. Pharm. Soc. Japan **52** (1932), 47), with Mg and HCl (*Willstätter*, Ber. **47**, 2874; *Willstätter* and *Mallison*, Ann. **408**, 27; *Combes*, C. r. **157**, 1454; *Willstätter* and *Mallison*, C. 1914 II 1358), and with Grignard reagents; the anthocyanidins can be converted by Zn and pyridine-acetic acid into their leucocompounds (III) (see *Kuhn* and *Winterstein*, Ber. **65**, 1742), and the catalytic hydrogenation of the flavones, etc., leads finally to the catechins (IV) (see *Freudenberg*, *Carrara* and *Cohn*, Ann. **446**, 87; *Freudenberg* and *Kammüller*, Ann. **451**, 209; *Freudenberg* and *Harder*, ibid. 213; *Freudenberg* and co-workers, Ann. **444**, 135; *Nierenstein*, J. Indian Chem. Soc. 8 (1931), 329):



Flavonol

Anthocyanidin salt

Anthocyanidin leucobase

Catechin

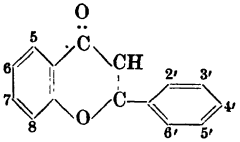
This formal connection makes it probable that the flavonols are the precursors of the anthocyanins (*Noack*, Z. Botanik **14** (1922), 1; *Karrer* and *Schwarz*, Helv. **11**, 916). Investigations on this point have in fact shown that the maximum formation of flavones is always observed before the occurrence of the anthocyanins, and that a rise in the content of anthocyanin is always accompanied by a corresponding decrease in flavone, their sum remaining practically constant. In the dying organism, the colouring matters are probably converted into catechins (*Klein* and *Werner*, Z. physiol. Chem. **143**, 9; *Onslow*, Nature **129** (1932), 601).

The presence of the phloroglucinol nucleus in all anthocyanins makes it clear why phloroglucinol is the only phenol which is necessary for anthocyanin formation, as has been shown by the experiments of *Czartowsky* on living plants.

The occurrence of several stages of hydroxylation, such as pelargonidin, cyanidin and delphinidin in one and the same plant (*Onslow*, loc. cit.; *G. Robinson* and *R. Robinson*, Biochem. J. **26**, (1932), 1647) is very striking, as is the simultaneous occurrence of methylated compounds (*Karrer* and *Widmer*, Helv. **10**, 5). Occasionally, nitrogenous members of this class of colouring matter are found in nature, such as the amino-anthocyanidin betanin, and the HCN derivative of a flavone, lotusin.

The colouring matters of this group are tabulated in the following pages, together with their aglycones and sugar components, and the more important references to the literature.

A. **Flavones**: nucleus



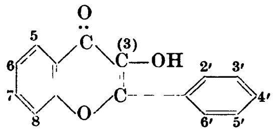
Glycoside: occurrence	Flavone	Sugar: Position ( )	Literature
Japanese primrose (*Primula modesta*)	Primetin, $C_{15}H_{10}O_4$, m.p. 231° (5:6-dihydroxy-flavone)	—	*Nagai* and *Hattori*, Acta phytochim. **5** (1930), 1
Toringin, $C_{21}H_{20}O_9$, m.p. 240°; *Pirus toringo* (Japan); poplar	Chrysin, $C_{15}H_{10}O_4$, m.p. 275° (5:7-dihydroxy-flavone)	Glucose	*Piccard*, Ber. **6**, 884; *Emilewicz*, *v. Kostanecki* and *Tambor*, Ber. **32**, 2448; *v. Kostanecki* and *Lampe*, Ber. **37**, 3167
Apiin, $C_{26}H_{28}O_{14}$, m.p. 228°; parsley (*Apium petroselinum*); celery	Apigenin, $C_{15}H_{10}O_5$, m.p. 347° (5:7:4′-trihydroxy-flavone)	Glucose, apiose	*v. Gerichten*, Ber. **9**, 1121; *Czajowski*, *v. Kostanecki* and *Tambor*, Ber. **33**, 1988; *Breger* and *v. Kostanecki*, Ber. **38**, 931; *Vongerichten*, Ann. **318**, 121; **321**, 74; *Schmidt*, Ann. **483**, 120
Acaciin (linarin), $C_{28}H_{32}O_{14}$, m.p. 260°; false acacia (*Robinia pseudacacia*); toadflax (*Linaria vulg.*)	Acacetin, $C_{16}H_{12}O_5$, m.p. 259° (4′-methyl ether of apigenin)	Disaccharide $C_{12}H_{22}O_{10}$ (glucose, rhamnose)	*Vongerichten*, Ber. **33**, 2904; *Perkin*, Proc. **16**, 45; J. **77**, 423; *Hattori*, Acta phytochim. **2** (1925), 99; *Merz* and *Wu*, Arch. Pharm. **274** (1936), 126
Chinese drug "yuen-hua" from *Daphne Genkwa*	Genkwanin, $C_{16}H_{12}O_5$, m.p. 286° (7-methyl ether of apigenin)	—	*Nakao* and *Tseng*, J. Pharm. Soc. Japan **52** (1932), 83, 148; *Mahal* and *Venkataraman*, Current Sci. **4** (1935), 311
Birch buds (*Betula*)	5-Hydroxy-7:4′-dimethoxy-flavone, $C_{17}H_{14}O_5$, m.p. 174° (Dimethyl ether of apigenin)	—	*Bauer* and *Dietrich*, Ber. **66**, 1053

A. Flavones (Continued)

Glycoside: occurrence	Flavone	Sugar: Position ( )	Literature
Galuteolin, $C_{21}H_{20}O_{11}$, m.p. 280°; *Galega off.*; dyer's rocket (*Reseda luteola*); foxglove (*Digitalis purpurea*)	Luteolin, $C_{15}H_{10}O_6$, m.p. 329° (5:7:3′:4′-tetrahydroxy-flavone)	Glucose	*Kiliani*, Ber. **32**, 2196; *v. Kostanecki, Rozycki* and *Tambor*, Ber. **33**, 3410; *Diller* and *v. Kostanecki*, Ber. **34**, 1449; *Kiliani* and *Mayer*, ibid. 3577; *Fainberg* and *v. Kostanecki*, Ber. **37**, 2625; *Barger* and *White*, Biochem. J. **17** (1923) 836; *Leon* and *Robinson*, J. **1931**, 2732; *Robinson* and *Leon*, Anal. fis. quím. **29** (1931), 415
Hydroxy-apiin-methyl ether, $C_{28}H_{32}O_{16}$; parsley	Hydroxy-apigenin methyl ether, m.p. 250° (4′-methyl ether of luteolin)	2 Glucose	*Vongerichten*, Ber. **33**, 2334; Ann. **318**, 136
Diosmin (barosmin), $C_{34}H_{44}O_{21}$, m.p. 280°; *Diosma crenata*; *Barosma* species	Hydroxy-apigenin methyl ether, m.p. 250° (4′-methyl ether of luteolin)	2 Glucose, rhamnose	*Oesterle* and *Wander*, Helv. **8**, 519
Lotusin, $C_{28}H_{31}O_{16}N$; *Lotus arabicus*	Lotoflavin, $C_{15}H_{10}O_6$, m.p. 200° (5:7:2′:4′-tetrahydroxy-flavone)	Maltose, HCN	*Dunstan* and *Henry*, Proc. Roy. Soc. **68**, 374; Chem. News **84**, 26
Skullcap (*Scutellaria baicalensis*)	Wogonin, $C_{16}H_{12}O_5$, m.p. 203° (5:7-dihydroxy-8-methoxy-flavone)	—	*Shibata, Iwata* and *Nakamura*, Acta phytochim. **1** (1923), 106; *Hattori*, ibid. **5** (1930), 99; **5** (1931), 219; *Hattori* and *Hayashi*, Ber. **66**, 1279
Baicalin, $C_{21}H_{18}O_{11}$, m.p. 223°; *Scutellaria baicalensis*	Baicalein, $C_{15}H_{10}O_5$, m.p. 265° (5:6:7-trihydroxy-flavone)	Glucuronic acid (6)	*Shibata, Iwata* and *Nakamura*, Acta phytochim. **1** (1923), 106; *Shibata* and *Hattori*, ibid. **5** (1930), 117; *Hattori*, ibid., **5** (1931), 219
Scutellarin, $C_{21}H_{18}O_{12}$, m.p. $>$310°; *Scutellaria* species	Scutellarein, $C_{15}H_{10}O_6$, m.p. $>$300° (5:6:7:4′-tetrahydroxy-flavone)	Glucuronic acid	*Molisch* and *Goldschmiedt*, Mo. **22**, 679; *Goldschmiedt* and *Zerner*, Mo. **31**, 439; *Wessely* and *Moser*, Mo. **56**, 97; *Wessely* and *Kallab*, Mo. **60**, 26; *Bargellini*, Gazz. **45**, I 69; *Robinson* and *Schwarzenbach*, J. **1930**, 822

Pectolinarin, $C_{29}H_{34}O_{15}$, m.p. 240–250°; toadflax (*Linaria vulg.*)	Scutellarein dimethyl ether, $C_{17}H_{14}O_6$ m.p. 218°; (5:7-dihydroxy-6:4′-dimethoxy-flavone)	Glucose, rhamnose	*Schmid* and *Rumpel*, Mo. **60**, 8; *Merz* and *Wu*, Arch. Pharm. **274** (1936), 126
Species of wheat (*Triticum dicoccum*)	Tricin, $C_{17}H_{14}O_7$, m.p. 291° (5:7:4′-trihydroxy-3:5′-dimethoxy-flavone)	—	*Allan* and *Robinson*, J. **125**, 2192; *Anderson* and *Perkin*, J. **1931**, 2624; *Badhwar*, *Kang* and *Venkataraman*; J. **1932**, 1107; *Anderson*, Canad. J. Res. **7**, 285; **9**, 80; *Gulati* and *Venkatamara*, J. **1933**, 942

B. **Flavonols**: nucleus



Glycoside: occurrence	Flavonol	Sugar: Position ( )	Literature
Fustin, $C_{36}H_{26}O_4$, m.p. 330°; fustic (*Rhus cotinus*); *Quebracho* tree	Fisetin, $C_{15}H_{10}O_6$, m.p. 219° (7:3′:4′-trihydroxy-flavonol)	1 Rhamnose	*v. Kostanecki*, *Lampe* and *Tambor*, Ber. **37**, 784; *v. Kostanecki* and *Nitkowski*, Ber. **38**, 3587; *v. Auwers* and *Pohl*, Ber. **48**, 85; *Perkin*, J. **71**, 1194; *Fonseka* and *Robinson*, J. **1931**, **2730**; *Robinson* and *Leon*, Anal. fis. quím. **29**, 415
False acacia wood (*Robinia pseudacacia*)	Robinetin, $C_{15}H_{10}O_7$, decomp. 325–330° (7:3′:4′:5′-tetrahydroxy-flavonol)	—	*Schmid* and *Pietsch*, Mo. **57**, 305; *Brass* and *Kranz*, N. **20**, 672; Ann. **499**, 175; *Schmid* and *Tadros*, Ber. **65**, 1689; *Charlesworth* and *Robinson*, J. **1933**, 268

B. Flavonols (Continued)

Glycoside: occurrence	Flavonol	Sugar: Position ( )	Literature
Galanga root (*Alpinia off.*)	Galangin, $C_{15}H_{10}O_5$, m.p. 218° (5:7-dihydroxy-flavonol)	—	*Herstein* and *v. Kostanecki*, Ber. **32**, 318; *v. Kostanecki* and *Tambor*, ibid. 2260; *v. Kostanecki*, *Lampe* and *Tambor*, Ber. **37**, 2803; *Chavan* and *Robinson*, J. **1933**, 368
Saponarin, $C_{21}H_{24}O_{12}.2H_2O$, m.p. 236°; soapwort (*Saponaria off.*)	Vitexin, $C_{15}H_{14}O_7$, m.p. 260° (6:7:4′-trihydroxy-2:3:6:7-tetrahydro-flavonol)	Glucose	*Perkin*, Proc. **16**, 44; J. **77**, 416; *Barger*, J. **89**, 1210; Ber. **35**, 1296
Datiscin, $C_{27}H_{30}O_{15}$, m.p. 190°; false hemp (*Datisca cannabina*)	Datiscetin, $C_{15}H_{10}O_6$, m.p. 276° (5:7:2′-trihydroxy-flavonol)	Glucose, rhamnose	*Leskiewicz* and *Marchlewski*, Ber. **47**, 1599; *Charaux*, C. r. **180**, 1419; *Kalff* and *Robinson*, J. **127**, 1968
Robinin, $C_{33}H_{40}O_{10}$, m.p. 197° and 250°; *Robinia pseudacacia*	Kampferol, $C_{15}H_{10}O_6$, m.p. 277° (5:7:4′-trihydroxy-flavonol)	2 Rhamnose, galactose	*v. Kostanecki* and *Tambor*, Ber. **37**, 792; *v. Kostanecki*, *Lampe* and *Tambor*, ibid. 2096; *Testoni*, Gazz. **30**, II 327; *Waliaschko*, Arch. Pharm. **247** (1909), 447; *Sando*, J. Biol. Chem. **94**, 675; *Zemplén* and *Gerecs*, Ber. **68**, 2054
Galanga root	Kampferide, $C_{16}H_{12}O_6$, m.p. 229° (kampferol 4′-methyl ether)	—	*Perkin* and *Wilson*, Proc. **18** (1902), 215
Fustic (*Morus tinctoria*); Indian jack-tree (*Atrocarpus integrifolia*)	Morin, $C_{15}H_{10}O_7$, m.p. 290° (5:7:2′:4′-tetrahydroxy-flavonol)	—	*v. Kostanecki*, *Lampe* and *Tambor*, Ber. **39**, 625; *Hlasiwetz* and *Pfaundler*, Ann. **127**, 351; *Bablishe* and *Perkin*, J. **69**, 792; *Robinson* and *Venkataraman*, J. **1929**, 61.

Kampferol is also the hydrolysis product of: multiflorin, $C_{27}H_{30}O_{15}$, m.p. 147–170° (polyantha rose, *Rosa multiflora*), with rhamnose and glucose, *Kondo*, *Iwamoto* and *Kuchiha*, J. Pharm. Soc. Japan **49** (1929), 35; kampferin, $C_{27}H_{30}O_{16}$, m.p. 195° (*Cassia angustifolia*), with 2 glucose, *Tutin*, J. **103**, 2006; kampferitrin, $C_{27}H_{30}O_{14}$, m.p. 203° (*Indigofera arreta*), with 2 rhamnose, *Perkin*, J. **91**, 435; and robinoside, m.p. 207° (white and blue periwinkle, *Vinca minor*), *Rabate*, Bull. Soc. Chim. Biol. **15** (1933), 130.

Quercitrin, $C_{21}H_{20}O_{11}$, m.p. 176°; *Quercus tinctoria*; horse chestnut, tea	Quercetin, $C_{15}H_{10}O_7$, m.p. 314° (5:7:3′:4′-tetrahydroxy-flavonol)	Rhamnose	*Herzig* and *v. Smoluchowski*, Mo. **14**, 53; *v. Kostanecki* and *Tambor*, Ber. **28**, 2303; **37**, 793; *v. Kostanecki*, *Lampe* and *Tambor*, ibid. 1402; *v. Kostanecki* and *Nitkowski*, Ber. **38**, 3587; *Asahina*, *Nakagome* and *Inubuse*, Ber. **62**, 3016; *Stein*, J. pr. **106**, 1; *Perkin*, J. **105**, 1408

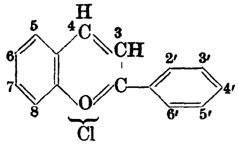
Quercetin occurs also as the hydrolysis product of:
quercimeritin (incarnatin, serotin), $C_{21}H_{20}O_{12}$, m.p. 245° (*Gossypium herbaceum*, *Trifolium incarnatum*, *Prunus serotina*), with glucose, *Perkin*, J. **95**, 2181; osyritrin, $C_{27}H_{30}O_{17}$, m.p. 185° (*Osyris compressa*), with 2 glucose, *Perkin*, J. **97**, 1776; myrticolorin, $C_{27}H_{28}O_{16}$, m.p. 185° (*Eucalyptus macrorrhyncha*), with 2 galactose, *Smith*, J. **73**, 697; *Perkin*, J. **97**, 1776; sophorin, $C_{27}H_{30}O_{16}$, m.p. 177° (*Sophora japonica*), with glucose and dulcitol, *Schmidt*, Arch. Pharm. **242** (1904), 210; *Foerster*, Ber. **15**, 214; violaquercitrin (rutin, globulariacitrin) $C_{27}H_{30}O_{16}$, m.p. 185–190° (*Viola tricolor* (pansy), *Ruta graveolens*, *Globularia alypum*, *Rhododendron rosmarinifolium*), with rhamnose and glucose, *Perkin*, J. **97**, 1776; *Willstatter* and *Zollinger*, Ann. **412**, 166; *Tiemann*, Arch. Pharm. **241** (1903), 297; *Nakaoki*, J. pharm. Soc. Japan **52** (1932), 198; *Charaux*, C. r. **178**, 1312; *Zemplén* and *Gerecs*, Ber. **67**, 2049; **68**, 1318

Xanthorhamnin, $C_{34}H_{44}O_{21}$; species of *Rhamnus*	Rhamnetin, $C_{16}H_{12}O_7$ (7-methyl ether of quercetin)	Rhamninose $C_{18}H_{34}O_{15}$	*Herzig*, Mo. **9**, 549; **12**, 172; **10**, 561; *Liebermann* and *Hormann*, Ann. **196**, 313; *Perkin*, J. **75**, 440; *Perkin* and *Allison*, J. **81**, 469; *Votoček* and *Frič*, C 1900 II 1180; *Robertson* and *Robinson*, J. **1927**, 2196.
Typha-glucoside, $C_{22}H_{22}O_{12}$; reedmace (*Typha angustata*); dyestuff "asbarg"; yellow wallflower	Isorhamnetin, $C_{16}H_{12}O_7$, m.p. 307° (3′-methyl ether of quercetin)	Glucose	*Heap* and *Robinson*, J. **1926**, 2336; *Fukuda*, Bull. Chem. Soc. Japan **3** (1928), 53
Rhamnazin, $C_{23}H_{24}O_{12}$; *Rhamnus* species	Rhamnazetin, $C_{17}H_{14}O_7$, m.p. 215° (7:3′-dimethyl ether of quercetin)	Glucose	*Perkin* and *Martin*, Proc. **1896/97**, 139; *Perkin* and *Allison*, Proc. **16**, 181
Cocoa beans	Cocoa red, $C_{17}H_{16}O_7$ (5:7:3′:4′-tetrahydroxy-6:8-dimethyl-2:3-dihydro-flavonol)	—	*Heiduschka* and *Bienert*, J. pr. **117**, 262

B. **Flavonols** (Continued)

Glycoside: occurrence	Flavonol	Sugar: (Position ( )	Literature
Myricitrin, $C_{21}H_{20}O_{12}$, m.p. 200°; *Myrica* species	Myricetin, $C_{15}H_{10}O_8$, m.p. 360° (5:7:3′:4′:5′-pentahydroxy-flavonol)	Rhamnose	*Nierenstein*, Ber. **61**, 361; *Perkin*, J. **81**, 203; *Shibata*, *Shibata* and *Kasiwagi*, Am. **41**, 208; *Charaux*, Bull. Soc. Chim. Biol. **6** (1924), 641; *Hattori* and *Hayashi*, Acta phytochim. **5** (1931), 213
Gossypitrin, $C_{21}H_{20}O_{13}$, m.p. 252°; Egyptian cotton flowers (*Gossypium herbaceum*)	Gossypetin, $C_{15}H_{10}O_8$, m.p. 313° (5:7:8:3′:4′-pentahydroxy-flavonol)	$C_6H_{12}O_6$	*Perkin*, J. **75**, 826; **95**, 1855; **103**, 650; **109**, 145; *Baker*, *Nodzu* and *Robinson*, J. **1929**, 74; *Neelakantam*, *Rao* and *Seshadri*, Proc. Indian Acad. Sci. **1** (1935) A, 887; **2**, 490
French marigold (*Tagetes patula*)	Quercetagetin, $C_{15}H_{10}O_8$ (5:6:8:3′:4′-pentahydroxy-flavonol)	—	*Perkin*, J. **103**, 209

C. **Anthocyanidins:** nucleus



Anthocyanin: occurrence	Anthocyanidin	Sugar: position ( )	Literature
Beetroot (*Beta vulg.*), *Atriplex hortensis*	Betanin chloride, $C_{15}H_{12}O_4NCl$ (3:5:7-trihydroxy-4′-amino-flavylium chloride)	—	*G. Robinson* and *R. Robinson*, J. **1932**, 1439; **1933**, 25
Gesnerin chloride, $C_{21}H_{21}O_9Cl$; *Gesnera fulgens*	Gesneridin chloride, $C_{15}H_{11}O_4Cl$ (5:7:4′-trihydroxy-flavylium chloride)	Hexose (5)	*G. Robinson* and *R. Robinson*, Nature **130**, 21

Pelargonin chloride, $C_{27}H_{31}O_{15}Cl$, m.p. 175–180°; geranium (*Pelargonium zonale*)	Pelargonidin chloride, $C_{15}H_{11}O_5Cl$ (3:5:7:4′-tetrahydroxy-flavylium chloride)	2 Glucose (3:5)	*Griffiths*, Ber. **36**, 3959; *Willstätter* and *Bolton*, Ann. **408**, 42; *Willstatter* and *Mallison*, ibid. 162; *Karrer* and *Widmer*, Helv. **10**, 67, 76; **11**, 837; *Karrer* and co-workers, ibid. **10**, 748; *Willstätter* and *Zechmeister*, C. 1914 II 1359; *Robinson* and *Robinson*, Nature **128**, 413; *Leon*, *Robertson*, *Robinson* and *Seshadri*, J. **1931**, 2672; *Robinson* and *Todd*, J. **1932**, 2488

Pelargonidin chloride is also the hydrolysis product of:

callistephin chloride, $C_{21}H_{21}O_{10}Cl$ (China aster, *Callistephus chinensis*), with glucose (3), *Willstatter* and *Burdick*, Ann. **412**, 149; *Robertson* and *Robinson*, J. **1928**, 1460; salvianin chloride, $C_{30}H_{33}O_{18}Cl$ (*Salvia coccinea*), with diglucose (3) and malonic acid, *Willstätter* and *Bolton*, Ann. **412**, 113; monardaein chloride, $C_{36}H_{37}O_{17}Cl$ (sweet bergamot, *Monarda didyma*), with diglucose (3) and p-hydroxy-cinnamic acid, *Karrer* and *Widmer*, Helv. **10**, 67.

Cyanin chloride, $C_{27}H_{31}O_{16}Cl$, m.p. 220°; cornflower (*Centaurea cyanus*); *Rosa gallica*	Cyanidin chloride, $C_{15}H_{11}O_6Cl$ (3:5:7:3′:4′-pentahydroxy-flavylium chloride)	2 Glucose (3:5)	*Willstätter* and *Everest*, Ann. **401**, 189, 227; *Willstätter* and *Nolan*, Ann. **408**, 1, 12; *Schmid* and *Huber*, Mo. **57**, 383; *Karrer* and *Pieper*, Helv. **13**, 1067; *Robinson* and *Robinson*, Nature **128**, 413; *Murakami*, *Robertson* and *Robinson*, J. **1931**, 2665; *Robinson* and *Todd*, J. **1932**, 2488

Cyanidin chloride is also the hydrolysis product of:

Keracyanin-(prunicyanin)-chloride, $C_{27}H_{31}O_{15}Cl$, from cherries and sloes, and *Ribes sanguineum*, with glucosido-rhamnose (3), *Willstatter* and *Zollinger*, Ann. **412**, 168; 175; *Robinson* and *Robinson*, Nature **128**, 413; *Murakami*, *Robertson* and *Robinson*, J. **1931**, 2665; mecocyanin chloride, $C_{27}H_{31}O_{15}Cl$, of the corn poppy (*Papaver rhoeas*), with gentiobiose (3), *Willstätter* and *Weil*, Ann. **412**, 237; *Robinson* and *Robinson*, Nature **128**, 413; *Murakami*, *Robertson* and *Robinson*, J. **1931**, 2665; *Grove*, *Inubuse* and *Robinson*, J. **1934**, 1608; chrysanthemin (asterin) chloride, $C_{21}H_{21}O_{11}Cl$, m.p. 205°, from *Chrysanthemum indicum*, elderberry (*Sambucus nigra*), beech (*Fagus sylvatica*), blackberry, China aster, with glucose (3), *Willstatter* and *Bolton*, Ann. **412**, 136; *Willstatter* and *Burdick*, ibid. 149; *Willstatter* and *Weil*, ibid. 248; *Nolan* and *Casey*, Proc. Roy. Irish Acad. **40** (1931), 56; *Murakami*, *Robertson* and *Robinson*, J. **1931**, 2665; *Robinson* and *Robinson*, Biochem. J. **26** (1932), 1647; *Robinson* and *Willstatter*, Ber. **61**, 2503; *Karrer* and *Pieper*, Helv. **13**, 1067; idaein chloride, $C_{21}H_{21}O_{11}Cl$, m.p. 210°, from the cowberry (*Vaccinium vitis idaea*), with galactose (3), *Willstatter* and *Mallison*, Ann. **408**, 15; *Grove* and *Robinson*, J. **1931**, 2722; hiviscin chloride, $C_{20}H_{19}O_{10}Cl$, m.p. 192°, from *Hiviscus babdariffa*, with a pentose (3), *Yamamoto* and *Osima*, Sci. Papers Inst. Phys. Chem. Res. Tokyo **19** (1932), 134.

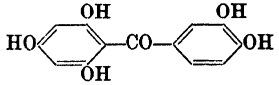
C. **Anthocyanidins** (Continued)

Anthocyanin: occurrence	Anthocyanidin	Sugar: Position ( )	Literature
Peonin chloride, $C_{28}H_{33}O_{16}Cl$, m.p. 165°; peony (*Paeonia off.*)	Peonidin chloride, $C_{16}H_{13}O_6Cl$ (3′-methyl ether of cyanidin chloride)	2 Glucose (3:5)	*Willstätter* and *Nolan*, Ann. **408**, 136; *Karrer* and *Widmer*, Helv. **10**, 8; *Nolan*, *Pratt* and *Robinson*, J. **1926**, 1968; *Robinson* and *Robinson*, Nature **128**, 413; *Robinson* and *Todd*, J. **1932**, 2488
Oxycoccicyanin chloride, $C_{22}H_{23}O_{11}Cl$; American cranberry (*Oxycoccus macrocarpus*)	Paeonidin chloride, $C_{16}H_{13}O_6Cl$ (3′-methyl ether of cyanidin chloride)	Glucose (3)	*Levy* and *Robinson*, J. **1931**, 2715; *Grove* and *Robinson*, Biochem. J. **25** (1931), 1706
Delphinin chloride, $C_{41}H_{39}O_{21}Cl$, m.p. 203°; larkspur (*Delphinium consolida*)	Delphinidin chloride, $C_{15}H_{11}O_7Cl$ (3:5:7:3′:4′:5′-hexahydroxyflavylium chloride)	2 Glucose, p-hydroxybenzoic acid	*Willstätter* and *Mieg*, Ann. **408**, 61; *Karrer* and *Widmer*, Helv. **10**, 567; *Karrer* and *Schwarz*, Helv. **11**, 916
Gentianin chloride, $C_{30}H_{27}O_{14}Cl$; gentian (*Gentiana acaulis*)	Delphinidin chloride, $C_{15}H_{11}O_7Cl$ (3:5:7:3′:4′:5′-hexahydroxyflavylium chloride)	Glucose, p-hydroxycinnamic acid	*Karrer* and *Widmer*, Helv. **10**, 73
Violanin chloride, $C_{36}H_{37}O_{18}Cl$; pansy (*Viola tricolor*)	Delphinidin chloride, $C_{15}H_{11}O_7Cl$ (3:5:7:3′:4′:5′-hexahydroxyflavylium chloride)	Glucose, rhamnose, p-hydroxycinnamic acid (3)	*Willstatter* and *Weil*, Ann. **412**, 178; *Karrer* and *de Meuron*, Helv. **16**, 292
Myrtillin chloride, $C_{22}H_{23}O_{12}Cl$; whortleberry (*Vaccinium myrtillus*)	Myrtillidin chloride, $C_{16}H_{13}O_7Cl$ (7-methyl ether of delphinidin chloride)	Galactose	*Willstätter* and *Zollinger*, Ann. **408**, 103; **412**, 204; *Karrer* and *Widmer*, Helv. **10**, 5
Althaein chloride, $C_{22}H_{23}O_{12}Cl$; hollyhock (*Althaea rosea*)	Myrtillidin chloride, $C_{16}H_{13}O_7Cl$ (7-methyl ether of delphinidin chloride)	Glucose	*Willstätter* and *Martin*, Ann. **408**, 110; *Kondo*, J. Pharm. Soc. Japan **50** (1930), 19
Petunin chloride, $C_{28}H_{33}O_{17}Cl$, m.p. 178°; *Petunia hybrida*	Petunidin chloride, $C_{16}H_{13}O_7Cl$ (3′-methyl ether of delphinidin chloride)	2 Glucose (3:5)	*Willstätter* and *Burdick*, Ann. **412**, 217; *Karrer* and *Widmer*, Helv. **10**, 5; *Bradley*, *Robinson* and *Schwarzenbach*, J. **1930**, 793; *Bell* and *Robinson*, J. **1934**, 1604; Biochem. J. **25** (1931), 168

Ampelopsin chloride, $C_{22}H_{23}O_{12}Cl$; Virginia creeper (*Ampelopsis quinquefolia*)	Ampelopsidin chloride, $C_{16}H_{13}O_7Cl$ (4′-methyl ether of delphinidin chloride)	Glucose	*Willstätter* and *Zollinger*, Ann. **412**, 213; *Karrer* and *Widmer*, Helv. **10**, 13
Oenin (syringin) chloride, $C_{23}H_{25}O_{12}Cl$; grape-vine (*Vitis vinifera*)	Oenidin (malvidin) chloride, $C_{17}H_{15}O_7Cl$ (3′:5′-dimethyl ether of delphinidin chloride)	Glucose (3)	*Willstätter* and *Zollinger*, Ann. **408**, 83; **412**, 206; *Karrer* and *Widmer*, Helv. **10**, 5; *Kondo*, J. Pharm. Soc. Japan **50** (1930), 20; *Levy*, *Posternak* and *Robinson*, J. **1931**, 2701
Malvin chloride, $C_{29}H_{35}O_{17}Cl$, decomp. 165°; common mallow (*Malva sylvestris*)	Malvidin (oenidin) chloride, $C_{17}H_{15}O_7Cl$ (3′:5′-dimethyl ether of delphinidin chloride)	2 Glucose (3:5)	*Willstätter* and *Mieg*, Ann. **408**, 122; *Karrer* and co-workers, Helv. **10**, 729; *Karrer* and *de Meuron*, Helv. **15**, 507; *Kondo*, J. Pharm. Soc. Japan **50** (1930), 20; *Robinson* and *Robinson*, Nature **128**, 413; *Robinson* and *Todd*, J. **1932**, 2299
Hirsutin chloride, $C_{30}H_{73}O_{17}Cl$; (*Primula hirsuta*)	Hirsutidin chloride, $C_{19}H_{19}O_7Cl$ (7:3′:5′-trimethyl ether of delphinidin chloride)	2 Glucose (3:5)	*Karrer* and *Widmer*, Helv. **10**, 758; *Levy* and *Robinson*, J. **1931**, 2738; *Robinson* and *Todd*, J. **1932**, 2293

e) BENZOPHENONE AND XANTHONE DERIVATIVES

The colour of the yellow wood from *Acacia catechu* is due to its content of **maclurin,** $C_{13}H_{10}O_6$, m.p. 122° (pentamethyl ether m.p. 157°) (*Ciamician* and *Silber*, Ber. **27**, 1628; **28**, 1394; *Nierenstein*, J. Indian Chem. Soc. **8**, 143). That its constitution can be represented by the formula



follows from the alkali degradation of its pentamethyl ether to phloroglucinol trimethyl ether and veratric acid, and from the oxidation products of leucomaclurin pentamethyl ether, which are 2:6-dimethoxy-p-quinone (see also p. 422) and veratraldehyde or veratric acid (*v. Kostanecki* and *Lampe*, Ber. **39**, 4014). The pentamethyl ether of maclurin can be obtained synthetically from phloroglucinol trimethyl ether and veratroyl chloride (*v. Kostanecki* and *Tambor*, ibid. 4022). Maclurin itself has been synthesised by the condensation of phloroglucinol with protocatechuic nitrile with the aid of $ZnCl_2$ and HCl (*Hoesch* and *v. Zarzecki*, Ber. **50**, 462).

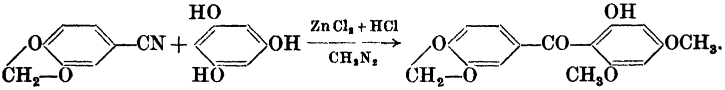
The South American coto bark from *Nectandra coto* contains a group of closely related yellow colouring matters: cotoin, hydrocotoin, methylhydrocotoin, protocotoin and the phenylcumalin and paracotoin already mentioned (p. 434).

Cotoin, $C_{14}H_{12}O_4$, m.p. 129° (dibenzoyl compound m.p. 136°), contains a methoxyl and a keto group, and is degraded by alkali to benzoic acid and phloroglucinol; hence it is a dihydroxy-methoxy-benzophenone (*Ciamician* and *Silber*, Ber. **27**, 409). The p-position of the methoxyl follows from the formation of a mono-nitroso-compound (*Pollak*, Mo. **22**, 996), and from the existence of only one methyl ether (*Späth* and *Wessely*, Mo. **49**, 229) and only one p-toluenesulphonate (*Karrer* and *Lichtenstein*, Helv. **11**, 789). It has been synthesised by the method of Hoesch from benzonitrile and phloroglucinol with subsequent methylation (*Hoesch*, Ber. **48**, 1131; *Späth* and *Fuchs*, Mo. **42**, 271).

Hydrocotoin, $C_{15}H_{14}O_4$, m.p. 118°, has been identified as cotoin monomethyl ether (2-hydroxy-4:6-dimethoxy-benzophenone) by its conversion into phenyl-coumarin acetate with acetic anhydride and sodium acetate. It has been prepared synthetically from benzoyl chloride and phloroglucinol dimethyl ether (*Pollak,* Mo. **18,** 738).

Methylhydrocotoin, $C_{16}H_{16}O_4$, m.p. 115°, has been synthesised from benzoyl chloride and phloroglucinol trimethyl ether, and hence is cotoin dimethyl ether (2:4:6-trimethoxy-benzophenone) (*Ciamician* and *Silber,* Ber. **27,** 1497).

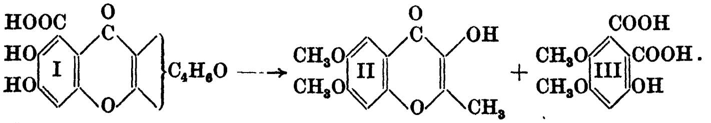
Protocotoin, $C_{16}H_{14}O_6$, m.p. 140°, is oxidised by $KMnO_4$ to acetopiperone; condensation with bromacetic ester yields a coumarone derivative, which shows the presence of a free ortho hydroxyl. It is therefore given the constitution: 2-hydroxy-4:6-dimethoxy-3′:4′-methylenedihydroxy-benzophenone, which is established by its synthesis by the method of Hoesch (*Spath* and *Bretschneider,* Mo. **49,** 429):



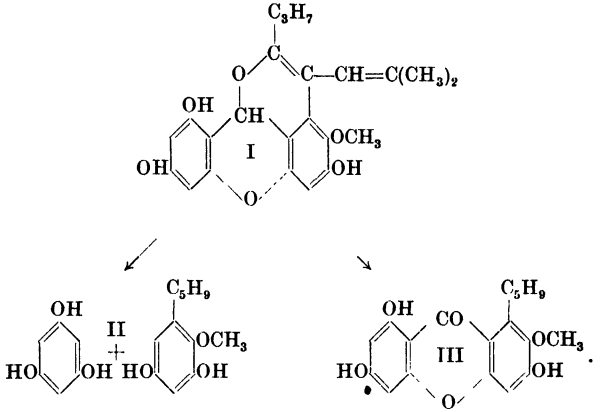
Euxanthic acid, $C_{19}H_{16}O_{10}\cdot 3H_2O$, m.p. 162°, is used as a pigment under the name of "Indian yellow". It is found in the urine of Indian cattle which have been fed on the leaves of *Mangifera indica* (*v. Kostanecki,* Ber. **19,** 2918). Hydrolysis gives **euxanthone,** $C_{13}H_8O_4$, a yellow compound m.p. 237°, identified as 3:5-dihydroxy-xanthone (*Baeyer,* Ann. **155,** 257; *Graebe,* Ber. **22,** 1405), and glucuronic acid, $C_6H_{10}O_7$ (*Spiegel,* Ber. **15,** 1964; *Baeyer,* loc. cit.). Euxanthone has been synthesised from β-resorcylic acid and hydroquinone-carboxylic acid (*Graebe,* loc. cit.), and from 2-chloro-6-methoxy-benzoic acid and hydroquinone monomethyl ether (*Ullmann* and *Panchaud,* Ann. **350,** 108). Indian yellow itself has been synthesised from euxanthone and acetobromo-glucuronic acid lactone (*Neuberg* and *Neimann,* Z. physiol. Chem. **44,** 115). The position of the glucose residue in the molecule follows from the hydrolysis of the pentamethyl ether, m.p. 168°, to 3-hydroxy-5-methoxyxanthone, $C_{14}H_{10}O_4$, m.p. 235°, and glucuronic acid trimethyl ether (*Robertson* and *Waters,* J. **1931,** 1709).

Gentisin, $C_{14}H_{10}O_5$, a sulphur-yellow compound, decomp. > 250°, the 2-monomethyl ether of gentisein (2:4:6-trihydroxyxanthone, $C_{13}H_8O_5$), an orange-yellow substance of m.p. 318°, *triacetate* m.p. 226°; see *v. Kostanecki* and *Tambor,* Mo. **15,** 1; *Hlasiwetz* and *Habermann,* Ann. **175,** 63; **180,** 343; *Shinoda,* J. **1927,** 1983), is found in gentian root (*Gentiana lutea*). It is prepared in a similar way to euxanthone, from phloroglucinol and hydroquinonecarboxylic acid (*v. Kostanecki* and *Tambor,* Mo. **15,** 1).

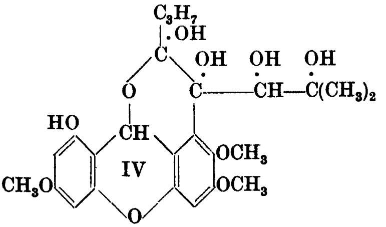
The yellow colouring matter **citromycetin** (I), $C_{14}H_{10}O_7\cdot 2H_2O$, m.p. 285° (diacetate m.p. 224°; dimethyl ether methyl ester m.p. 178°), from cultures of species of *Citromyces,* can be decarboxylated to citromycin, $C_{13}H_{10}O_5$, m.p. 290° (diacetate m.p. 222°); potash fusion of the dimethyl ether of the latter converts it into 3-hydroxy-6:7-dimethoxy-2-methyl-benzo-γ-pyrone (II), m.p. 180°, and 3-hydroxy-5:6-dimethoxy-phthalic acid (III), m.p. 182°. With HI the latter yields 2:4:5-trihydroxy-benzoic acid, m.p. 209°, which on rapid heating gives hydroxy-hydroquinone, m.p. 140·5°. These reactions, which show the constitution of the greater part of the molecule of the pigment, can be expressed by the following formulae (*Hetherington* and *Raistrick,* Phil. Trans. **220** (1931) B, 1):

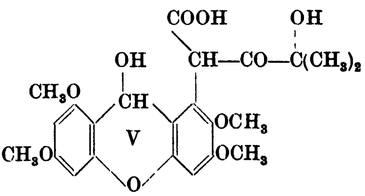


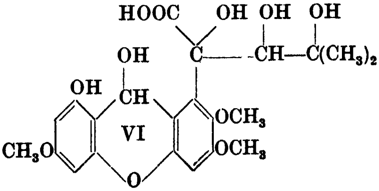
Mangostin (I), $C_{23}H_{24}O_6$, m.p. 181°, the yellow colouring matter of the skin of the fruit of *Garcinia mangostana,* contains two olefinic double bonds (tetrabromide; tetrahydro-compound m.p. 151°), three phenolic hydroxyls (trimethyl ether m.p. 100°; triacetate m.p. 115°), and one methoxyl group; two of its oxygen atoms show no characteristic reactions and must be present as ether links (*Dragendorff*, Ann. 482, 280). The following fragments of a side-chain were isolated from the products of fusion with KOH or treatment with alcoholic KOH: acetic acid, isoamyl alcohol, isovaleric acid and methylheptenol (idem, ibid.). Permanganate oxidation and ozonolysis yielded acetone and α-hydroxy-isobutyric acid, while tetrahydromangostin gave isocaproic acid (idem, Ann. 487, 62). The other alkali fission products of mangostin are phloroglucinol (see II), $C_6H_6O_3$, m.p. 215° (*Yamashiro*, Bull. Chem. Soc. Japan 7 (1932), 1), a phenol $C_{12}H_{16}O_3$, which has been identified as 1-amylenyl-2-methoxy-3:5-dihydroxybenzene (see II) (*Murakami*, Proc. Imp. Acad. Tokyo 7 (1931), 254), and a yellow compound $C_{19}H_{18}O_6$, m.p. 212°, the chemical character, stability and colour reactions of which indicate that it is a xanthone derivative (III). The formation of these various compounds leads to formula (I) for mangostin (*Murakami*, Ann. 496, 122):



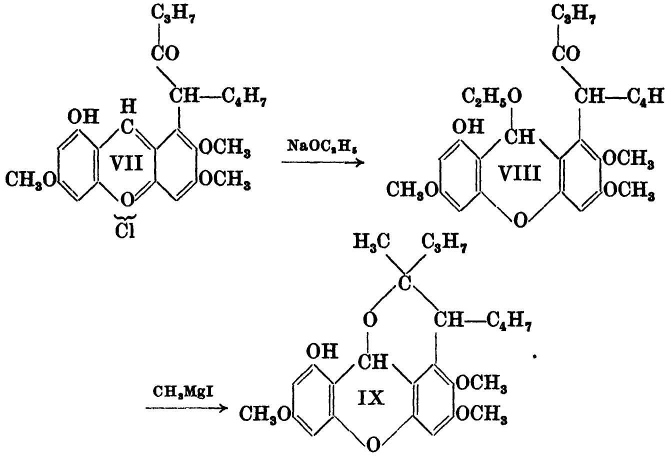
This receives further confirmation from the permanganate oxidation of mangostin dimethyl ether to the neutral compound (IV), $C_{25}H_{30}O_{10}$, m.p. 225° (containing 5 active H-atoms, and 3 OCH_3), of mangostin trimethyl ether to the keto-acid (V), $C_{23}H_{26}O_{10}$, m.p. 240° (oxime decomp 100°), and of acetyl-mangostin dimethyl ether to the hydroxy-acid (VI), $C_{22}H_{26}O_{11}$, m.p. 123° (lactone m.p. 199°):

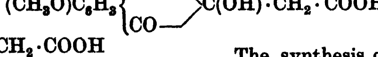


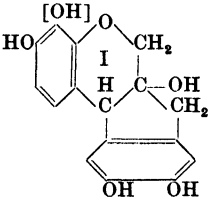


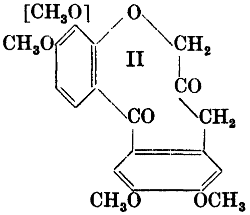


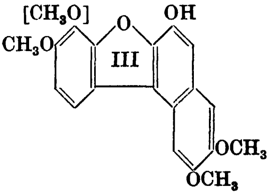
The orange-yellow hydrochloride (decomp. 157°) of mangostin dimethyl ether, $C_{25}H_{28}O_6$, must be regarded as the oxonium compound (VII); with Na ethoxide it yields the corresponding colourless ethoxy derivative (VIII), m.p. 158°, which with CH_3MgI undergoes ring closure to methyl-dihydromangostin dimethyl ether (IX), $C_{28}H_{32}O_6$, m.p. 141°; the latter is also colourless (*Murakami*, Proc. Imp. Acad. Tokyo 7 (1931), 311).

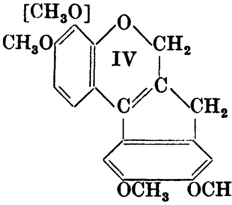


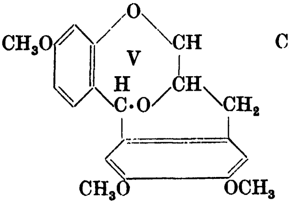
Brasilin (I), $C_{16}H_{14}O_5$, is the colouring matter of Brazilian, Pernambuco or red wood from *Caesalpinia brasiliensis*. It crystallises in white needles with $1^1/_2$ mol. of water, and its solution in alkali absorbs oxygen from the air and becomes bright carmine red. Addition of acids to this solution precipitates brasilein, $C_{16}H_{12}O_5 \cdot H_2O$, which is also formed by the action of iodine upon brasilin; it can be reconverted into brasilin by reduction, best of its acetyl compound (cf. *Herzig* and *Pollak*, Ber. **36**, 3951; Mo. **25**, 871). Brasilein is thus related to brasilin as a dyestuff is to its leuco-compound. Brasilin forms mono-, di-, tri- and tetra-alkyl ethers (*Schall*, Ber. **27**, 524; *Herzig*, Mo. **15**, 139; **16**, 906), while brasilein gives, besides the normal di- and tri-alkyl ethers, tri- and tetra-alkyl brasileinol by the addition of one mol. of water (*Engels*, *Perkin* and *Robinson*, J. **93**, 1115). Distillation of brasilin gives a large amount of resorcinol (cf. haematoxylin). If a current of air is passed into a strongly alkaline solution of brasilin for some time, 3:7-dihydroxy-γ-chromone, $C_9H_6O_4$, is formed (*Pfeiffer* and *Oberlin*, Ber. **57**, 208). The oxidation of trimethyl-brasilin, $C_{16}H_{10}O(OH)(OCH_3)_3$, m.p. 140°, with $KMnO_4$ yields various acids, in particular, 5-methoxy-2-carboxyphenoxyacetic acid, $(CH_3O)C_6H_3\left\{\begin{matrix}OCH_2\cdot COOH\\ COOH\end{matrix}\right.$, 4:5-dimethoxy-2-carboxy-phenylacetic acid, $(CH_3O)_2C_6H_2\left\{\begin{matrix}CH_2\cdot COOH\\ COOH\end{matrix}\right.$, m-hemipinic acid, $(CH_3O)_2C_6H_2(COOH)_2$, brasilic acid,  $(CH_3O)C_6H_3\left\{\begin{matrix}OCH_2\\ CO\end{matrix}\right\rangle C(OH)\cdot CH_2\cdot COOH$, and brasilinic acid, $(CH_3O)C_6H_3\left\{\begin{matrix}OCH_2\cdot COOH\\ CO\cdot C_6H_2(OCH_3)_2\cdot COOH\end{matrix}\right.$. The synthesis of brasilinic acid was of great importance in establishing the structure of brasilin: it was first obtained by condensing m-hemipinic anhydride with m-methoxy-phenoxy-acetic ester by means of $AlCl_3$ (*Perkin* and *Robinson*, Proc. **23** (1907), 291: **24** (1908), 54; J. **93**, 489), and later from veratroyl chloride and methoxy-phenoxypropionic ester (*Rây*, *Silooja* and *Wadha*, J. Indian Chem. Soc. **10** (1933), 617). The dehydration product of brasilic acid, anhydro-brasilic acid, $C_{12}H_{10}O_5$, has also been synthesized (*Perkin* and *Robinson*, loc. cit.). Oxidation of trimethyl-brasilin with chromic acid gives a ketone, trimethyl-brasilone (II), $C_{19}H_{18}O_6$, which is converted by nitric acid into nitro-hydroxy-dihydro-trimethyl-brasilone, $C_{19}H_{19}O_7(NO_2)$; this by continued treatment with alkali gives methoxy-salicylic acid, $(CH_3O)C_6H_3(OH)COOH$, and nitro-homoveratrol, $O_2N{\cdot}C_6H_2{\cdot}CH_3(OCH_3)_2$. Trimethyl-brasilone is readily dehydrated into trimethyl-anhydro-brasilone (III), $C_{19}H_{16}O_5$, which behaves in every respect like a derivative of β-naphthol: it couples with diazonium solutions to give azo-dyes, and with HNO_3 it gives a nitro-compound, from which by reduction followed by oxidation an ortho-quinone, corresponding to β-naphthaquinone, can be obtained: this is trimethoxy-α-brasan-quinone, $C_{19}H_{14}O_6$ (*Perkin* and *Robinson*, J. **95**, 381). With HI or conc. H_2SO_4 trimethyl-brasilone undergoes isomeric change, apparently into derivatives of ββ-phenylene-naphthylene-oxide (brasane) (*Perkin*, J. **81**, 1008; *v. Kostanecki* and *Paul*, Ber. **35**, 2609; *v. Kostanecki* and *Lloyd*, Ber. **36**, 2193; *Herzig* and *Pollak*, Ber. **37**, 631; Mo. **23**, 165). Reduction of trimethyl-brasilone with phenylhydrazine yields trimethyl-anhydro-brasilin (IV); catalytic reduction converts the latter into trimethyl-desoxy-brasilin (trimethyl-dihydro-anhydro-brasilin), which with CrO_3 is oxidised back into trimethyl-brasilone (II) (*Perkin*, *Rây* and *Robinson*, J. **1926**, 941; **1927**, 2094; **1928**, 1504; *Pfeiffer*, *Angern*, *Haack* and *Willems*, Ber. **61**, 839, 1923):

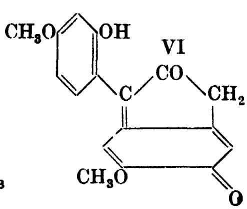

I


II


III


IV

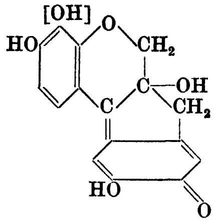

V


VI

Trimethyl-anhydro-brasilin has been synthesised in the following way: resorcinol monomethyl ether and β-chlorpropionic acid give 7-methoxy-chromanone, which can be condensed with vanillin methyl ether to 3-(3′:4′-dimethoxy-benzal)-7-methoxy-chroman-4-one. This compound, after reduction, can be dehydrated and cyclised with P_2O_5 to trimethyl-anhydro-brasilin (*Pfeiffer* and *Oberlin*, Ber. **60**, 2142; cf. *Pfeiffer* and *Willems*, Ber. **62**, 1243).

Trimethyl-brasilone is reduced by Na amalgam to trimethyl-allo brasilin (V), $C_{19}H_{20}O_5$, α-form m.p. 135–136°, β-form m.p. 143·5°, which can be degraded to 2-(2′-hydroxy-4′-methoxy-benzyl)-4:5-dimethoxy-benzoic acid, m.p. 222–224° (methyl ester m.p. 159°) (see *Pfeiffer* and *Schneider*, J. pr. **140**, 9).

On the basis of the results which have been described and because of the formation of 3:7-dihydroxy-γ-chromone (see above) in the atmospheric oxidation of alkaline brasilin, and of the oxidation of trimethyl-desoxy-brasilin to the quinone (VI), $C_{17}H_{14}O_5$, red needles of m.p. 241° (together with trimethyl-brasilone), the following formula has been attributed to the quinonoid colouring matters brasilein and haematein (hydroxy-brasilein, see below) (idem, ibid. **144**, 54):



Haematoxylin [I][1], $C_{16}H_{14}O_6 \cdot 3H_2O$ (hydroxy-brasilin), is found in logwood or Campeachy wood, the heartwood of *Haematoxylon campechianum.* It forms yellowish crystals, with a sweet taste, and dissolves in alkali to give a violet-blue solution. The logwood dyeing industry is based upon the production of dark-blue shades by means of iron and chromium lakes. When an ammoniacal solution of haematoxylin is allowed to stand in the air, haematein-ammonia, $C_{16}H_{11}(NH_4)O_6$, is formed, from which acetic acid precipitates the free haematein, $C_{16}H_{12}O_6$, as a red-brown substance, which after drying has a metallic lustre (*Erdmann* and *Schultz,* Ann. **216**, 236). Haematoxylin gives penta-alkyl ethers and a penta-acetyl-compound. Distillation or fusion with potash yields pyrogallol (*Meyer,* Ber. **36**, 1561), and atmospheric oxidation of an alkaline solution gives 3:7:8-trihydroxy-γ-chromone (*Pfeiffer, Oberlin* and *Konermann,* Ber. **58**, 1947; cf. brasilin). Oxidation of tetramethyl-haematoxylin with $KMnO_4$ gives acids which are analogous to those obtained from trimethyl-brasilin, e.g. dimethoxy-phenoxy-acetic-o-carboxylic acid, $(CH_3O)_2C_6H_2\left\{\begin{matrix}OCH_2\cdot COOH\\ COOH\end{matrix}\right.$, m-hemipinic acid and haematoxylinic acid, corresponding to brasilinic acid (see p. 454). In the same way oxidation of tetramethyl-haematoxylin with CrO_3 gives tetramethyl-haematoxylone [II], which corresponds to trimethyl-brasilone, and gives analogous degradation products (*Perkin,* J. 81, 1057; *v. Kostanecki* and *Rost,* Ber. **36**, 2202). Further the corresponding transformations of tetramethyl-haematoxylone into tetramethyl-anhydro-haematoxylone [III], tetramethyl-anhydro-haematoxylin [IV], and tetramethyl-desoxy-haematoxylin are also known (*Pfeiffer, Angern, Haack* and *Willems,* Ber. **61**, 839). Haematoxylin [I] differs, therefore, from brasilin (I) only in the presence of a hydroxyl group in one benzene ring. The synthesis of tetramethyl-anhydro-haematoxylin from pyrogallol-1:2-dimethyl ether, β-chlorpropionic acid and vanillin methyl ether has been carried out in a way similar to that used for the corresponding brasilin derivative (*Pfeiffer, Haack* and *Willems,* Ber. **61**, 294).

f) NITROGENOUS HETEROCYCLIC NATURAL COLOURING MATTERS

The class of the

Pyrrole Colouring Matters[2]

includes the very important respiratory and oxidation catalysts (blood pigment, cytochrome, catalase and peroxidase), the blood pigments of several marine animals (chlorocruorin, haemocyanin and the ascidian pigments), the natural porphyrins (ooporphyrin, uroporphyrin, coproporphyrin and conchoporphyrin), the pyrromethene pigments (the bile pigment bilirubin, the uteroverdin of dogs' placentae, stercobilin and copronigrin from faeces, the shell-pigment of birds' eggs oocyan, the bacterial pigment prodigiosin, and the chromoproteids of red algae), and finally the green assimilating pigments of plants, chlorophyll a and b.

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[1] The formulae in this paragraph are those above with the addition of the substituent shown in square brackets.

[2] *H. Fischer* and *H. Orth,* Die Chemie des Pyrrols. Leipzig, Vol. I, 1934; Vol. II, 1937.

Haemoglobin has a molecular weight of 69,000 (see *v. Mutzenbecher*, Z. angew. Chem. **44**, 121; *Zeile*, Biochem. Z. **258**, 347; *Svedberg* and *Eriksson-Quensel*, Am. **56**, 1700), and its non-protein component, which is the prosthetic group and has a red colour, is **haemin,** $C_{34}H_{32}O_4N_4FeCl$ (formula I, p. 458). The constitution of this compound has been determined by analytical degradation and by synthesis, as a result of the experience gained in the study of the natural porphyrins (see p. 461) and the biologically related bile pigments (see p. 463).

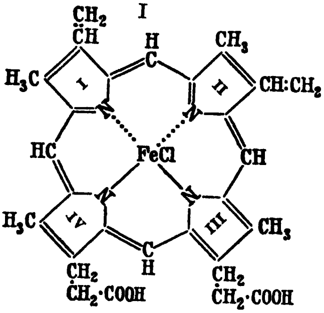
For the preparation of the purest haemoglobin solutions by electro-dialysis, see *Ettisch* and *Groscurth*, Biochem. Z. **266**, 441.

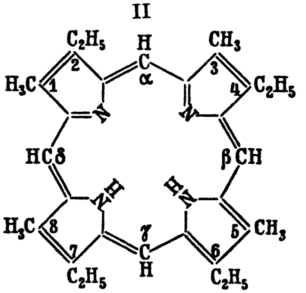
The natural blood pigment is derived from the halogen-free haemochromogen, $C_{34}H_{34}O_4N_4Fe$, which is sensitive to oxygen and contains labile divalent iron; the crystalline *haemin* (I), $C_{34}H_{32}O_4N_4FeCl$ (with trivalent iron), the ionised chlorine atom of which can be replaced by OH with the formation of haematin, $C_{34}H_{32}O_4N_4FeOH$, is formed by a secondary reaction in the treatment of the protein with NaCl-acetic acid (*Nencki*, Ber. **29**, 2877; *Kuster* and *Fuchs*, Ber. **40**, 2021; *Willstätter* and *Pfannenstiel*, Ann. **358**, 213). That the oxygen atoms are present as carboxyl groups is established by the formation of a dimethyl ester, m.p. 262° (*Kuster*, Z. physiol. Chem. **82**, 113). Two vinyl groups can be saturated by catalytic reduction with Pd-H_2 to give mesohaemin, $C_{34}H_{36}O_4N_4FeCl$ (*Fischer* and *Rose*, ibid. **91**, 181; *Fischer* and *Putzer*, ibid. **154**, 39).

Treatment of haemin and its nearest derivatives with HI-acetic acid (*Zaleski*, ibid. **43**, 11; *Nencki* and *Zaleski*, Ber. **34**, 997), or, better, with HCOOH + Fe (*Willstätter* and *Fischer*, Z. physiol. Chem. **87**, 423; *Fischer* and *Putzer*, ibid. **154**, 39), leads to the removal of the Fe atom, and this process can be reversed (*Willstätter* and *Fischer*, ibid. 87, 482; *Fischer* and *Putzer*, ibid. **154**, 57; *Fischer*, *Treibs* and *Zeile*, ibid. **195**, 1; *Treibs*, ibid. **212**, 26). Such treatment leads to the porphyrins, which are distinguished by a characteristic absorption spectrum and are widely distributed in the plant and animal kingdoms (see p. 461). Haemin itself gives protoporphyrin, $C_{34}H_{34}O_4N_4$ (dimethyl ester m.p. 228°). The iron is also removed when the blood pigment is allowed to putrefy for a short time (*Kämmerer's porphyrin*, see *Fischer* and *Schneller*, ibid. **130**, 316; **135**, 268; *Fischer*, *Kammerer* and *Kuhner*, ibid. **139**, 108; *Fischer* and *Lindner*, ibid. **145**, 203); the action of bacteria for several months in a solution which is alkaline with sodium carbonate brings about complete removal of the unsaturated side-chains, with the formation of *deuteroporphyrin*, $C_{30}H_{30}O_4N_4$ (dimethyl ester m.p. 220°), the structure of which is shown by its oxidation (idem, ibid. **161**, 18) to citraconimide (formula VII, p. 458) and haematinic acid, and by its synthesis (*Fischer* and *Kirstahler*, Ann. **466**, 178). When the iron is removed by HBr-acetic acid, the elements of water are added to both vinyl groups to give *haematoporphyrin* $C_{34}H_{38}O_6N_4$ (dimethyl ester dimethyl ether m.p. 165°; synthesis: *Fischer* and *Zeile*, Ann. **468**, 98); this reaction can be reversed, and protoporphyrin and haemin obtained from haematoporphyrin (*Fischer* and *Lindner*, Z. physiol. Chem. **142**, 141). Gentle action of HI upon haemin removes the iron, and also brings about a reduction which is analogous to that of haemin into mesohaemin, mesoporphyrin, $C_{34}H_{38}O_4N_4$, being formed (dimethyl ester m.p. 217°). Further reduction of the latter with Na amalgam removes the uninterrupted conjugation of the double bonds of the porphin nucleus, which is the cause of the colour, and gives the colourless mesoporphyrinogen, $C_{34}H_{44}O_4N_4$, which contains "true" pyrrole nuclei.

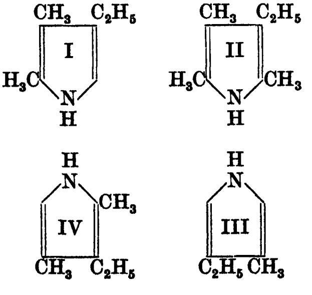
For the synthesis of isomeric mesoporphyrins, see *Fischer* and *Kirrmann*, Ann. **475**, 266.

The decarboxylation of mesoporphyrin (*Willstätter* and *Fischer*, Z. physiol. Chem. **87**, 423) gives the fundamental substance of haemin, aetioporphyrin III (formula II), $C_{32}H_{38}N_4$, decomp. 335° (1:3:5:8-tetramethyl-2:4:6:7-tetraethyl-porphin; cf. also chlorophyll-aetioporphyrins, p. 468).

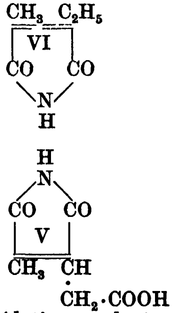

I


II

The complete reduction of the blood pigment with HI-acetic acid (*Fischer* and *Bartholomäus*, Ber. **45**, 467, 1980; *Fischer* and *Eismayer*, Ber. **47**, 1820) finally yields the simple units of the structure, haemopyrrole (I), phyllopyrrole (II), opsopyrrole (III) and cryptopyrrole (IV), together with their carboxylic acids (*Piloty*, Ann. **366**, 237; *Fischer* and *Treibs*, Ann. **450**, 132; *Fischer* and *Bartholomäus*, Ber. **45**, 1315; *Piloty* and *Dormann*, ibid. 2592; *Fischer* and *Rose*, Ber. **47**, 791), but if the molecule is broken down with methylating agents, the only product is phyllopyrrole and its carboxylic acids (idem, Z. physiol. Chem. **87**, 39). Oxidation of haemin gives two molecules of haematinic acid (V), from the acid pyrrole nuclei, while mesoporphyrin, with the basic pyrrole nuclei stabilised by saturation of the side-chains, also gives two molecules of methyl-ethyl-maleinimide (VI) (see *Küster*, Ber. **35**, 2948; **40**, 2017).



Reduction products



Oxidation products

The determination of the molecular weight of haemin (*Fischer* and *Hahn*, Ber. **46**, 2308), and the yield of pyrrole derivatives obtained from its fission, point to a complex formula with four pyrrole nuclei. *H. Fischer* and his school were able to build up the porphin skeleton from synthetic pyrrole bases via the corresponding methenes. The porphyrins so obtained agree perfectly in their absorption spectra with the natural iron-free pigments and with the compounds prepared from haemin and its derivatives by removal of the iron. The earlier constitutional formulae proposed (cf. pyrrindole formula, *Piloty* and *Dormann*, Ann. **388**, 313; *Piloty* and *Stock*, Ann. **392**, 215; tetraindolyl-complex formula, *Nencki* and *Zaleski*, Ber. **34**, 997; tetrapyrrylethylene, *Willstätter*, Ber. **47**, 2863; *Fischer* and *Beller*, Ann. **444**, 238; dipyrryl-methene complex salt, *Fischer* and *Schubert*, Ber. **56**, 1202; tetrapyrryl-methene, *Fischer* and *Scheyer*, Ann. **489**, 185) have therefore been discarded, and that first proposed by *W. Küster* (Z. physiol. Chem. **82**, 463) has been firmly established by the synthetical work of *H. Fischer* (with *Zeile*, Ann. **468**, 106). After the positions of the substituents on the porphin nucleus had been proved by the synthesis of mesoporphyrin (*Fischer* and *Stangler*, Ann. **459**, 65), the way to the synthesis of protoporphyrin and hence of haemin became clear (*Fischer* and *Zeile*, Ann. **468**, 98; *Fischer*, *Treibs* and *Zeile*, Z. physiol. Chem. **193**, 138; *Fischer*, N. **17**, 616).

The catalytic action of haemin in the oxidation of various biologically important classes of substances is of great interest (lipoids, see *Kuhn* and *Meyer*, Z. physiol. Chem. **185**, 193; *Kuhn* and *Braun*, Ber. **59**, 2370; *Robinson*, Biochem. J. **18**, 255; protein components, see *Harrison*, Biochem. J. **18**, 1009; *Bergel* and *Bolz*, Z. physiol. Chem. **215**, 33; *Warburg* and *Brefeld*, Biochem. Z. **145**, 461; *Warburg*, Ber. **58**, 1001; carbohydrates, see *Warburg* and *Christian*, Biochem. Z. **238**, 131; *v. Euler*, *Fink* and *Hellström*, Z. physiol. Chem. **169**, 10). Its action as a peroxidase is weaker than that of haemoglobin.

The iron-containing pigment of haemoglobin can form compounds with certain gases (O_2) which dissociate easily (oxyhaemoglobin, see *Nencki* and *Sieber*, Ber. **19**, 128; *Haurowitz*, Z. physiol. Chem. **186**, 147), and this property enables it to carry oxygen in the organism from the lungs to the sites of oxidation, and to carry off the combustion product (CO_2) back to the respiratory organs. The poisonous action of carbon monoxide and nitrous fumes is due to the displacement of the oxygen in these compounds, since haemoglobin can form similar compounds with CO and nitrous fumes (carboxy-haemoglobin, nitroxy-haemoglobin), which are more stable and decomposed only by the action of light. Oxyhaemoglobin has a peroxidase action (*Willstatter* and *Pollinger*, ibid. **130**, 281; *Bach* and *Kultjugin*, Biochem. Z. **167**, 227).

Under certain conditions the oxidation of oxyhaemoglobin (*Haurowitz*, Z. physiol. Chem. **194**, 98) and of haemoglobin (*Denes*, Biochem. Z. **223**, 481; *Warburg* and *Kubowitz*, ibid. **227**, 184; *Warburg*, *Kubowitz* and *Christian*, ibid. **233**, 240; *Schuler*, ibid. **255**, 474; *Clark* and *Pickett*, Am. **52**, 465) gives methaemoglobin, which has one atom of oxygen more than haemoglobin and contains iron in the trivalent state. For the equilibrium between haemoglobin, methaemoglobin and oxyhaemoglobin, see *Heubner* and *Rhode*, Arch. exp. Path. **100** (1923), 117; *Ferry*, J. Biol. Chem. **59**, 295.

Experiments by Warburg with methylene blue, the oxidation of which is used as a model of respiration, have indicated that methaemoglobin is the oxygen donor in the process (*Warburg*, *Kubowitz* and *Christian*, Biochem. Z. **221**, 494; **227**, 245; *Michaelis* and *Salomon*, ibid. **234**, 107; *Warburg* and *Christian*, ibid. **238**, 131):

$$\begin{tikzcd}
\text{Haemoglobin (Fe}'') \arrow[r] & \text{Methaemoglobin (Fe}''') \arrow[r, dashed, "\text{oxid org. subst.}"] & \text{Haemoglobin} \\
+\ \text{pigment} & +\ \text{leuco-compound} \arrow[l, bend left, "\text{atmospheric oxygen}"] &
\end{tikzcd}$$

Very great biological importance attaches to the group of haemin-enzymes, cytochrome, the oxygen-carrier of respiration, catalase and peroxidase, which are compounds closely related in structure to haemin.

Cytochrome, discovered by *MacMunn* in 1886, is found in the tissues of numerous organs (brain, heart, kidney, liver etc., see *Bierich*, *Rosenbohm* and *Kalle*, Z. physiol. Chem. **164**, 207; *Hohnes*, Biochem. J. **24** (1930), 914), in glands (thymus, thyroid, see *Bierich*, *Rosenbohm* and *Kalle*, loc. cit.), in the tissue of tumours (*Bierich* and *Rosenbohm*, Z. physiol. Chem. **155**, 249), in yeast (*Keilin*, Proc. Roy. Soc. B **98**, 312; **104**, 206), and in bacteria (*Yaoi* and *Tamiya*, Proc. Imp. Acad. Tokyo **4** (1928), 436), etc.

This enzyme which, like the oxygen-carrying enzyme of Warburg, takes part in the respiration of animal and plant cells (*v. Euler*, *Nilsson* and *Runehjelm*, Z. physiol. Chem. **169**, 123; *Keilin*, loc. cit.; *Tamiya* and *Tanaka*, Acta phytochimica **5** (1930), 167), consists of three haemochromogen components (*Fischer* and *Hilmer*, Z. physiol. Chem. **153**, 195; *v. Euler* and *Fink*, ibid. **164**, 69; *Fischer* and *Schwerdtel*, ibid. **175**, 248; *Bierich* and *Rosenbohm*, ibid. **184**, 246; *v. Euler* and *Hellström*, ibid. **190**, 189).

Synthetic products obtained by adding nitrogenous bases to the vinyl groups of protoporphyrin have a spectrum which is identical with the component C of cytochrome (*Zeile*, ibid. **207**, 35; *Zeile* and *Piutti*, ibid. **218**, 52). By the reduction of its porphyrin component into mesoporphyrin-ester it is proved to be of the aetioporphyrin III type (see p. 458; *Zeile* and *Reuter*, ibid. **221**, 201).

For a spectroscopic method of distinguishing between the most important cultures of yeast, based upon their cytochrome content, see *Fink*, ibid. **210**, 197.

The **oxygen-carrying respiratory ferment** of *Warburg*, which is present, not only in the organisms of the higher animals (heart muscle), but also in bacteria (acetic and azoto bacteria), in fungi (yeast), and in plants (potato), is distinguished from the accompanying cytochrome, not merely by the position of its absorption bands (*Warburg* and *Negelein*, Biochem. Z. **202**, 202; *Warburg* and *Kubowitz*, ibid. **203**, 95; *Warburg* and *Negelein*, ibid. **204**, 495), but also by its special affinity for oxygen, by the formation of an inactive CO-compound which is sensitive to light (*Warburg*, N. **15**, 546; **16**, 345, 856; *Negelein* and *Gerischer*, N. **21**, 884), and by the fact that its action is poisoned by HCN (*Alt*, Biochem. Z. **221**, 498). The molecular weight of the enzyme is of the order of 60,000 (*Svedberg* and *Eriksson*, N. **21**, 330).

The significance of the respiratory enzyme lies in its activation of the oxygen necessary for cell-respiration. The process which takes place in aerobic systems is as follows (*Warburg*, *Negelein* and *Haas*, ibid. **266**, 1; *Haas*, N. **22**, 207):

$$O_2 \rightarrow \underset{\text{(oxygen-carrying ferment)}}{\text{Ferro} \rightarrow \text{Ferri}} \rightarrow \cdots \rightarrow \underset{\text{(cytochrome, shortest wavelength component)}}{\text{Ferro} \rightarrow \text{Ferri}} \rightarrow \cdots \text{ Substrate}$$

The prosthetic group of the Warburg ferment is most closely related chemically to those haemins which seem to have two colours and which appear green or red according to the thickness of the layer (e.g. phaeoporphyrin, phaeohaemin); they are reduction products of chlorophyll and oxidation products of the blood pigment. The intermediate position of this substance, which has been shown experimentally with the closely related spirographis-haemin (p. 461), is an important argument in favour of the common origin of haemin and chlorophyll (*Warburg*, Z. angew. Chem. **45**, 1).

Catalase, a substance widely distributed in animal and plant tissues (*Issajev*, Z. physiol. Chem. **42**, 102; **44**, 546; *v. Euler* and *Josephson*, Ann. **452**, 158; **455**, 1), has the important function of destroying the hydrogen peroxide formed in the cells by dehydrogenation processes (*Wieland*, Ber. **55**, 3639); its activity for this purpose is about 1000 times greater than that of colloidal Pt or of haemin (*Kuhn* and *Brann*, Ber. **59**, 2370). After reduction it shows the haemochromogen spectrum (*Zeile* and *Hellström*, Z. physiol. Chem. **192**, 171; *Zeile*, ibid. **195**, 39). Carbon monoxide is a specific poison for the enzyme (*Califano*, N. **22**, 249).

The elementary particle of this enzyme appears from its velocity of diffusion to possess the dimensions of a haemoglobin molecule (*Zeile*, Biochem. Z. **258**, 347; *Stern*, Z. physiol. Chem. **217**, 237).

Catalase systems can be prepared artificially and the combination haemin-catalase-piperazine has by far the largest activity (idem, ibid. **219**, 105).

Peroxidase, prepared from horse-radish (*Willstätter* and *Stoll*, Ann. **416**, 21; *Willstätter*, Ann. **422**, 47; *Willstätter* and *Pollinger*, Ann. **430**, 290), plays a part in the oxidation processes in the plant organism, and, like cytochrome and catalase, is poisoned by CO, HCN, hydrazine, etc. (*Elliott* and *Sutter*, Z. physiol. Chem. **205**, 47; *Wieland* and *Sutter*, Ber. **61**, 1060). Spectroscopic investigation shows that it is a catalyst of the haemin class (*Kuhn*, *Hand* and *Florkin*, N. **19**, 771; Z. physiol. Chem. **201**, 255). Its activity as a peroxidising agent is usually measured in terms of the quantity of the red colouring matter purpurogallin which it produces from pyrogallol (see p. 425).

The haemoglobins from the warm and cold blooded land animals yield the same haemin, but the blood pigments of some marine animals are different from this in composition.

Chlorocruorin is a green colouring matter which contains protein and occurs in the blood of many annelids (*Spirographis*); from it there can be obtained the substance **spirographis-haemin,** $C_{33}H_{30}O_5N_4FeCl$. This contains two carboxyl groups and an aldehyde group which forms an oxime (*Griffiths*, C. r. **114**, 1277; *Warburg* and *Negelein*, Biochem. Z. **202**, 202; **214**, 64; **227**, 171; **244**, 9, 239; *Fox*, Nature **130**, 92). When oxidised with atmospheric oxygen, it gives a green substance similar to chlorophyll (*Warburg*, Z. angew. Chem. **45**, 1; *Warburg* and *Negelein*, ibid. 350). In its prosthetic porphyrin, which is derived from aetioporphyrin III, a vinyl group can be detected by the action of diazoacetic ester. According to the results of *Fischer* and *v. Seemann*, spirographis-haemin should be formulated as haemin (cf. p. 458) in which the vinyl group on pyrrole nucleus I has been degraded to an aldehyde group (Z. angew. Chem. **49**, 461).

The blue blood of crustaceae, molluscs (*Helix*, *Busycon*, *Octopus*, *Loligo*) and cephalopods (*Limulus*, *Homarus*) contains haemocyanin, in which a copper-containing pigment **haemocuprin** is combined with protein (*Hernler* and *Philippi*, Z. physiol. Chem. **191**, 23, 28; *Schmitz*, ibid. **194**, 232; **196**, 71; *Hernler* and *Philippi*, ibid. **216**, 110). The molecular size of the chromoproteid from *Octopus vulgaris* has been shown to be of the order of 2,000,000 from results with the ultra-centrifuge (*v. Mutzenbecher*, Z. angew. Chem. **44**, 121; *Karrer*, ibid. **46**,3 7; *Svedberg* and *Hetroth*, Am. **51**, 539; *Svedberg* and *Erikson*, Nature **130**, 434; Am. **54**, 4730; *Svedberg*, N. **22**, 225).

Haemocyanin, in which the copper is in the cuprous state, needs vigorous oxidising agents, such as $KMnO_4$, to convert it into methaemocyanin, which contains divalent copper; the latter can be reduced again with $K_4Fe(CN)_6$. In the presence of atmospheric oxygen it forms oxyhaemocyanin or oxymethaemocyanin, and both of these oxidation-reduction systems are distinguished by a high potential (*Conant*, *Chow* and *Schoenbach*, J. Biol. Chem. **101**, 463).

The brown **ascidian-pigment** from the blood corpuscles of *Ascidia mentula*, *Phallusia mannillata*, contains about 10% of vanadium (*Henze*, Z. physiol. Chem. **72**, 494; **79**, 215; **86**, 340). The chromogen, in which the metal is divalent (idem, ibid. **213**, 125), possibly serves for the assimilation of carbon dioxide which is used for the formation of the "tunicin"; this is a kind of cellulose and is the material of which the skeleton of the animal is constructed (*Zechmeister* and *Tóth*, ibid. **215**, 267).

Porphyrins are often encountered in the animal kingdom, e.g. in the young organism (embryos, skeleton of young mammals), under pathological conditions (cf. uro- and copro-porphyrin), in the Harderian gland of rodents, in hedgehog bristles, as pigment of the feathers (turacin) and the eggs (ooporphyrin) of birds, and as the pigment of mussel shells (conchoporphyrin). In vertebrates the porphyrins seem to be formed mainly in the bone-marrow (*Fischer*, Ber. **60**, 2629); they are also found in the plant kingdom and in fungi (yeast). Mesoporphyrin and its decarboxylation product meso-aetioporphyrin are contained in small quantities in oil shale and asphalts, and in mineral oils, together with porphyrins of vegetable origin (see under chlorophyll, p. 471).

They produce sensitising effects in the organism, as in the case of paramaecia (*Infusoria*) (*Fischer* and *v. Kemnitz*, Z. physiol. Chem. **96**, 309; *Fischer*, ibid. **97**, 109), and in porphyria cause an increase in the oxygen used (*Gaffron*, N. **13**, 859; Biochem. Z. **179**, 158); they also influence the contractibility of muscle (Klin. Woch. **1927**, no. 14). For the sensitivity of rats to light after the administration of haematoporphyrin (*Nencki*) and its behaviour in the animal body, see *Hutschenreuter*, Z. physiol. Chem. **222**, 161.

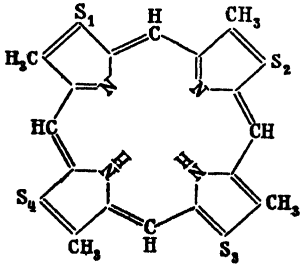
For their isolation and separation, the method of ether-HCl fractionation of *Willstätter* has proved to be of great value (cf. chlorophyll). Porphyrins can be recognised by their characteristic band spectra (cf. *Treibs*, Ann. **476**, 1) and their pH-fluorescence curves are also useful for distinguishing between them (*Fink*, N. **17**, 388; *Fink* and *Weber*, N. **18**, 16; *Fink*, Biochem. Z. **211**, 65; *Mayer*, Z. physiol. Chem. **177**, 48; *Fink* and *Hoerburger*, ibid. **202**, 8; **218**, 181; **220**, 123). The m.ps. of their methyl esters are important constants for purposes of comparison. Because of their large molecular weights it is often difficult to determine accurately the number of hydrogen atoms in the molecule by ordinary methods; in such cases measurement of the heat of combustion is useful (*Stern* and *Klebs*, Ann. **505**, 295).

While haemin is derived from aetioporphyrin III (cf. also chlorophyll), most of the natural porphyrins are derived from aetioporphyrin I.

Ooporphyrin, $C_{34}H_{32}O_4N_4$ (*dimethyl ester* m.p. 228°), which is found in the spotted egg-shells of various birds, e.g. seagulls and plovers (*Fischer*, Z. physiol. Chem. **97**, 168; *Fischer* and *Kögl*, ibid. **131**, 241; **138**, 262; *Fischer* and *Lindner*, ibid. **142**, 142; *Fischer* and *Muller*, ibid. 156), is identified as protoporphyrin (Kammerer's porphyrin) by its conversion into meso- and haemato-porphyrin and into haemin.

Under pathological conditions, e.g. in porphyria (*Fischer* and co-workers, ibid. **150**, 44), animal ochronosis (*Fink*, ibid. **197**, 193; *Fink* and *Hoerberger*, ibid. **202**, 8), and in many cases of poisoning (e.g. by sulphonal, lead compounds), the organism produces in particular **uroporphyrin,** $C_{40}H_{38}O_{16}N_4$ (formula below, $S_{1-4} = CH_2 \cdot CH(COOH)_2$; *octamethyl ester* m.p. 293°; see *Nebelthau*, ibid. **27**, 324; *Fischer*, ibid. **95**, 34; **98**, 78; *Fischer* and *Hilger*, ibid. **140**, 231) and **coproporphyrin I,** $C_{36}H_{38}O_8N_4$ (formula below, $S_{1-4}{=}CH_2CH_2COOH$; *tetramethyl ester* m.p. 250°, see *Fischer*, ibid. **96**, 148; **98**, 14; synthesis: *Fischer* and *Treibs*, Ann. **450**, 132; *Fischer* and *Andersag*, Ann. **458**, 139; *Fischer* and co-workers, Ann. **466**, 147).

Coproporphyrin also occurs in yeast (*Fischer* and *Schneller*, ibid. **135**, 253; *Fischer* and *Hilger*, ibid. **138**, 55; *Fischer* and *Fink*, ibid. **144**, 101; **150**, 244) and in plants (*Fischer* and *Schwerdtel*, ibid. **159**, 120).



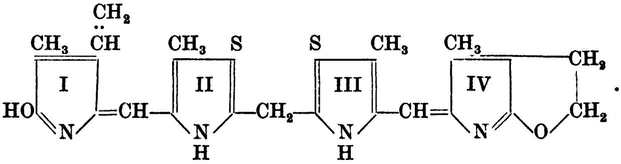
Coproporphyrin is oxidised exclusively to haematinic acid (formula V, p. 458); on reduction it gives no pyrrole bases, but only haemo-pyrrole-carboxylic acids. The evidence that these two porphyrins have the structure shown in the formula above comes from experiments both of degradation and of synthesis; their close relationship is shown by the partial decarboxylation of uroporphyrin into coproporphyrin I (*Fischer*, Z. physiol. Chem. **97**, 116; *Fischer* and *Zerweck*, ibid. **137**, 242; *Fischer* and *Hilger*, ibid. **149**, 66) and the conversion of both into aetioporphyrin I (1:3:5:7-tetramethyl-2:4:6:8-tetraethyl-porphin), m.p. 394° (*Fischer* and *Hilger*, ibid. **140**, 223).

Turacin, $C_{40}H_{36}O_{16}N_4Cu$, the red pigment from the wing feathers of the African bird *Turacus*, has been recognised as the copper salt of uroporphyrin (idem, ibid. **138**, 49, 55).

An isomer of coproporphyrin, coproporphyrin III (1:3:5:8-tetramethyl-porphin-2:4:6:7-tetra-propionic acid; methyl ester m.p. 145° or 172°) has also been observed in cases of porphyria (*Hijmans* and *Bergh*, C. 1929 II 2686; synthesis: *Fischer*, *Platz* and *Morgenroth*, Z. physiol. Chem. **182**, 265; *Fischer* and *Hierneis*, ibid. **196**, 155; *Fischer* and *Riedl*, Ann. **482**, 216).

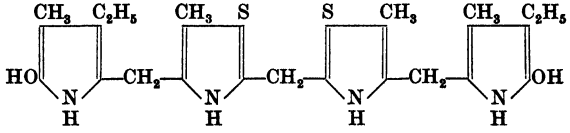
The occurrence of porphyrins such as **conchoporphyrin,** $C_{37}H_{38}O_{10}N_4$ (formula above, $S_1{=}CH_2{\cdot}CH{\cdot}(COOH)_2$, $S_{2-4}{=}CH_2CH_2COOH$; pentamethyl ester m.p. 273°; degradation to coproporphyrin I, see *Fischer* and *Jordan*, Z. physiol. Chem. **190**, 75) and uroporphyrin (*Fischer* and *Haarer*, ibid. **204**, 101) in mussel-shells (*Pteria radiata*), apparently in the form of their calcium salts, is of interest.

An appreciable amount of the blood pigment is decomposed in the organism, principally in the spleen (*London* and *Kryzanowskaja*, ibid. **227**, 229), the iron being eliminated and the porphin ring opened. The α-methine carbon atom of the haemin is also lost, and there is formed the yellowish-red bile-pigment **bilirubin** (haematoidin), $C_{33}H_{36}O_6N_4$ (dimethyl ester of the enol-form m.p. 205°, of the keto-form, m.p. 169°, see *Küster*, ibid. **141**, 40) (*Fischer*, ibid. **73**, 216; *Fischer* and *Reindel*, ibid. **127**, 299); *Siedel* and *Fischer*, ibid. **214**, 145):



Bilirubin ($S = CH_2{\cdot}CH_2{\cdot}COOH$).

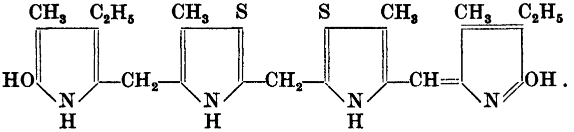
The pigment is carried by the bile into the intestine where it suffers bacterial reduction to mesobilirubinogen (urobilinogen), $C_{33}H_{44}O_6N_4$, m.p. 197—200° (see *Fischer*, ibid. **78**, 222; *Fischer* and *Meyer*, ibid. **75**, 342; *Fischer* and *Niemann*, ibid. **127**, 325; **137**, 307):



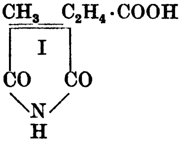
Mesobilirubinogen

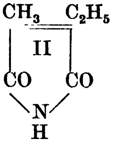
This compound in the normal way is ejected in the faeces, together with another reduction product, stercobilin (see p. 465); in liver diseases, however, it occurs in large quantities in the urine (*Fischer* and *Meyer-Betz*, ibid. **75**, 232), where by the action of oxygen it is at once oxidised to urobilin (synthesis: *Siedel* and *Meier*, ibid. **242**, 101).

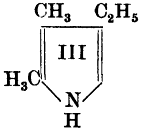
When the reduction process is imitated with Na amalgam as reducing agent, a yellow intermediate stage, dihydro-mesobilirubin, m.p. 278–284°, can be isolated (*Fischer* and *Baumgartner*, ibid. **216**, 260):

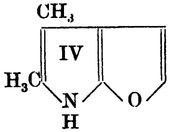


The pyrrole nature of the original bile-pigment was shown much earlier by the oxidation to haematinic acid (I) (*Kuster*, ibid. **59**, 63; Ber. **35**, 1268) and of the tetrahydro-compound, mesobilirubin, to methyl-ethyl-malein-imide (II), together with haematinic acid (*Piloty* and *Thannhauser*, Ann. **390**, 191); this established at the same time the existence of its vinyl groups, as in haemin. The end nucleus IV of the pyrrole chain was obtained by reduction with HI as haemopyrrole (III), and by the action of nitrous acid as the so-called "nitrite body" (IV) (the Gmelin reaction) (*Fischer* and *Hess*, Z. physiol. Chem. **194**, 195, 207):



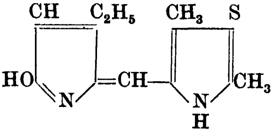






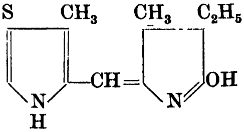
The absence of an absorption spectrum with four bands excludes the possibility that the pyrrole nuclei of the bile pigments are united in a porphin ring as in the porphyrins. At the same time the compounds cannot be given the structure of tetrapyrryl-ethylenes, because of the Gmelin reaction with nitrous acid. Detailed investigation of mesobilirubin settled the question of the constitution in favour of that of an unbranched chain of pyrrole components.

The degradation of mesobilirubin by fusion with resorcinol or by treatment with potassium methoxide led to a mixture of the following four acids, the constitutions of which have been established by synthesis (*Fischer* and *Hess*, ibid. **194**, 195; *Fischer* and *Adler*, ibid. **200**, 213; *Fischer*, *Yoshioka* and *Hartmann*, ibid. **212**, 146; *Siedel* and *Fischer*, ibid. **214**, 145), and by fission to known mono-nuclear pyrrole derivatives (*Fischer* and *Rose*, ibid. **89**, 256; Ber. **45**, 1581; 3274; *Piloty* and *Thannhauser*, Ann. **390**, 191):



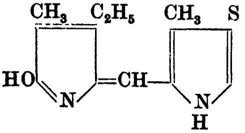
Xanthobilirubic acid
$C_{17}H_{22}O_3N_2$, m.p. 290° (methyl ester m.p. 212°)

+



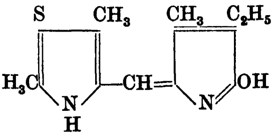
Iso-neo-xanthobilirubic acid
$C_{16}H_{20}O_3N_2$, m.p. 242° (methyl ester m.p. 205°)

and



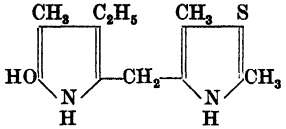
Neo-xanthobilirubic acid
$C_{16}H_{20}O_3N_2$, m.p. 246° (methyl ester m.p. 174°

+



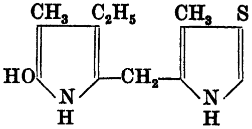
Iso-xanthobilirubic acid
$C_{17}H_{22}O_3N_2$, m.p. 289° (methyl ester m.p. 198°).

Xanthobilirubic acid and neo-xanthobilirubic acid are reduced by HI to



Bilirubic acid
$C_{17}H_{24}O_3N_2$, m.p. 188°

and



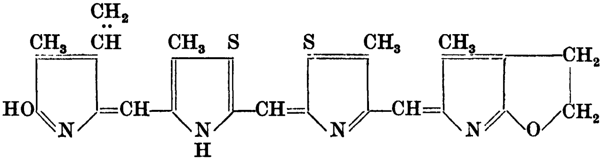
Neo-bilirubic acid
$C_{16}H_{22}O_3N_2$, m.p. 179°

which can be obtained as the main product in the direct reduction of the bile pigment, and have been prepared synthetically (*Fischer* and *Adler*, Z. physiol. Chem. **197**, 237).

When neo-xanthobilirubic acid had been synthesised (idem, ibid. **200**, 213; *Fischer* and *Siedel*, ibid. **214**, 145), it was possible to attempt the synthesis of a compound of symmetrical structure of the mesobilirubin type (mesobilirubin IIIα); condensation of 2 mol. of neo-xanthobilirubic acid with 1 mol. of formaldehyde gave an isomer of mesobilirubin which showed remarkable similarity in its properties with those of the mesobilirubin from the bile pigment (*Fischer* and *Hess*, ibid. **194**, 203; *Fischer* and *Adler*, ibid. **200**, 209).

For the synthesis of **coprobilirubin**, $C_{35}H_{40}O_{10}N_4$, m.p. 292° (tetramethyl ester dihydrochloride m.p. 200°), which is derived from coproporphyrin IV, and is based upon aetioporphyrin IV, see idem, ibid. **210**, 139.

Uteroverdin, $C_{33}H_{34}O_6N_4$ (dimethyl ester, m.p. 209°), the green colouring matter of dogs' placentae (*Lemberg* and *Barcroft*, Proc. Roy. Soc. B **110**, 362), is known by spectroscopic analysis and by its conversion into bilirubic acid (see above) with HI-acetic acid to be similar to the bile pigments (*Lemberg*, Ann. **499**, 25). It is formed when bilirubin is dehydrogenated with ferric chloride in acetic acid, and is hence held to be dehydro-bilirubin (idem, ibid.; *Siedel* and *Fischer*, Z. physiol. Chem. **214**, 157):

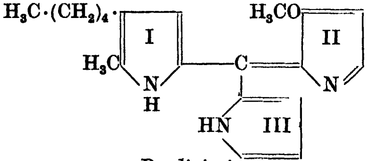


Uteroverdin

Normal and pathological faeces contain, in addition to the coproporphyrin already mentioned, the optically active **stercobilin**, $C_{33}H_{46}O_6N_4$, m.p. 236°, which is degraded by oxidation to haematinic acid and gives the same reduction products as bilirubin (*Watson*, ibid. **204**, 57; **208**, 101; **221**, 145; *Fischer* and *Halbach*, ibid. **238**, 59; *Siedel* and *Meier*, ibid. **242**, 101), and also **copronigrin**, $C_{42}H_{55}O_{14}N_3$.

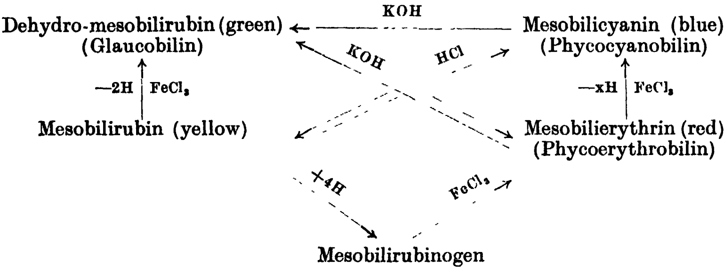
The blue-green pigment of many egg-shells, **oocyan**, (dimethyl ester $C_{28}H_{31}O_6N_3$, m.p. 234°), which is a tripyrrene, also belongs to the bile pigment series (*Fischer* and *Lindner*, ibid. **145**, 216; *Lemberg*, Ann. **488**, 74). It gives the *Gmelin* reaction.

The red pigment from cultures of *Bacillus prodigiosus* (*Gorbach*, C. 1930 I 1484), **prodigiosin**, $C_{20}H_{25}ON_3$, forms leaflets with a metallic lustre, and its zinc complex salt, $(C_{20}H_{24}ON_3)_2Zn$, m.p. 176°, and the perchlorate, $C_{20}H_{25}ON_3 \cdot HClO_4$, crystallise readily. The compound can be characterised as a tripyrryl-methene derivative by its absorption spectrum and by the properties of its Zn salt. The presence of one methoxyl has been shown by the method of *Zeisel*, and a *Zerevitinoff* estimation gives two reactive hydrogen atoms (*Wrede* and *Hettche*, Ber. **62**, 2678). Distillation of the pigment with soda-lime yields 2-methyl-3-n-amyl-pyrrole, $C_{10}H_{17}N$ (from ring I) (*Wrede*, Z. physiol. Chem. **210**, 125; *Wrede* and *Rothhaas*, ibid. **226**, 95); oxidation with H_2O_2 gives methoxy-maleinimide, $C_5H_5O_3N$, m.p. 169° (from ring II) (idem, ibid. **215**, 67). When reduced catalytically with Pd-charcoal, it takes up 14 H; the oxidation of the product with $KMnO_4$ in acid solution gives the pyrrolidine derivative, $C_{10}H_{21}N$, which corresponds to the above pyrrole, α-pyrrolidine-carboxylic acid, oxamic acid and succinic acid; the presence of the latter, and the formation of maleinimide (with methoxy-maleinimide) in the chromic acid oxidation of prodigiosin itself, shows the presence of an unsubstitituted pyrrole nucleus (III) in the molecule of the pigment. These results lead to the following formula for prodigiosin (*Wrede* and *Rothhaas*, ibid. **219**, 267; **222**, 203; **226**, 95):



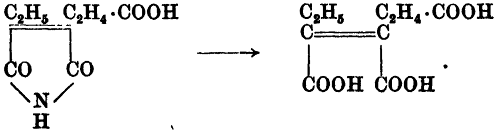
Prodigiosin

The red algae, *Nori* and *Ceramium*, contain the chromoproteids phycoerythrin and phycocyan, the molecular weights of which, according to sedimentation experiments, are of the order of 200,000 (*Svedberg* and *Katsurai*, Am. **51**, 3573; *Svedberg* and *Eriksson*, Am. **54**, 3998). Removal of the protein component yields the pigments **phycoerythobilin** and **phycocyanobilin**, which are closely related to the bile pigments (*Kylin*, Z. physiol. Chem. **69**, 169; **83**, 171; **197**, 1; *Boresch*, Biochem. Z. **119**, 167; *Lemberg*, ibid. **219**, 255; Ann. **461**, 46; **477**, 195). The mutual relationship of the pigments and their reversible conversion into bilirubin derivatives of known constitution is shown in the following scheme (*Lemberg* and *Bader*, N. **21**, 206; *Lemberg*, Ann. **505**, 151):



It is interesting to notice that the algae pigments belong to the meso type in which two of the pyrrole nuclei carry ethyl substituents, a type to which chlorophyll (see p. 467) also belongs, while the animal pigments, haemin (p. 457) and bilirubin (p. 463), contain two pyrrole nuclei in which a vinyl group is a substituent.

The **pigment** of the alga *Rhodymenia palmata* is oxidised to the following two fission products, which are like those obtained from pyrrole pigments (*Levene* and *Schormüller*, J. Biol. Chem. **93** (1931), 571):



Rufescin, the red pigment of the mussel, *Haliotis rufescens*, can be converted by HCl, via haliotirubin, into haliotiverdin and halioticyanin, which are very similar to the bile pigments bilicyanin and urobilin. Reduction with Na amalgam gives a hydro-compound which is related spectroscopically to hydrobilirubin (*Dhéré* and *Baumeler*, C. 1930 II 418).

Chlorophyll[1]

The green colouring matter of leaves, chlorophyll, has been considered briefly in vol. I, p. 752; recently, however, considerable progress has been made in the investigation of this important pigment, so that it seems necessary to summarise the results obtained.

Natural chlorophyll consists of two waxy organic pigments each of which contains four pyrrole nuclei and also magnesium. Both are esters of a dicarboxylic acid with methyl alcohol and phytol ($C_{20}H_{40}O$, see vol. I):

Chlorophyll a: $C_{54}H_{72}N_4O_5Mg$ or $(C_{32}H_{30}ON_4Mg)COOCH_3 \cdot COOC_{20}H_{39}$
Chlorophyll b: $C_{54}H_{70}N_4O_6Mg$ or $(C_{32}H_{28}O_2N_4Mg)COOCH_3 \cdot COOC_{20}H_{39}$

The ratio of the two pigments in the leaves of almost all terrestrial and aquatic plants is about 3:1. They were separated by *Willstätter* by their differing solubilities in petroleum ether and aqueous methanol (*Willstätter* and *Stoll*, Ann. **387**, 317; *Willstätter* and *Isler*, Ann. **390**, 269; *Stoll* and *Wiedemann*, Helv. **16**, 739), and can also be separated by selective adsorption on clay and other colloids (*Tswett*, Ber. deut. bot. Ges. **24**, 234, 316, 384; Ber. **41**, 1352; **43**, 3139; **44**, 1124), or, better, on cane sugar (*Winterstein* and *Stein*, Z. physiol. Chem. **220**, 263). With the Mg-free pigments the separation can also be carried out by the ether-hydrochloric acid method because of their different basicities (*Willstätter* and *Mieg*, Anm. **350**, 1; *Willstätter* and *Isler*, Ann. **380**, 154).

Mild fermentative hydrolysis of the chlorophylls in aqueous acetone by the enzyme chlorophyllase which is contained in the leaves (*Borodin*, Bot. Z. **40**, 608; *Willstätter* and *Benz*, Ann. **358**, 267; *Willstatter* and *Stoll*, Ann. **378**, 18) leads to a loss of phytol, and gives the crystalline chlorophyllides a $C_{32}H_{30}ON_4Mg.COOCH_3 \cdot COOH$ (b similarly). In methyl alcohol, on the other hand, esterification to the corresponding dimethyl esters takes place, and the methyl-chlorophyllides a and b are obtained. Mild action of alkali hydrolyses the methyl ester groups, with the formation of the free dicarboxylic acids, the *chlorophyllins*: a $C_{32}H_{30}ON_4Mg(COOH)_2$, and b.

Dilute mineral acids at first eliminate the magnesium[2] (*Willstatter* and *Fritzsche*, Ann. **371**, 33), forming the phaeophytins, a $C_{32}H_{32}ON_4 \cdot COOCH_3 \cdot COOC_{20}H_{39}$, and b $C_{32}H_{30}O_2N_4 \cdot COOCH_3 \cdot COOC_{20}H_{39}$, while conc. HCl hydrolyses the esterified carboxyls one after the other. Thus the elimination of phytol gives phaeophorbide a,

$$C_{32}H_{32}ON_4 \cdot COOCH_3 \cdot COOH^3$$

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[1] For a more detailed discussion of the constitution, see *Linstead*, Ann. Rep. Chem. Soc. **1935**, 359; **1937**, 375.

[2] This can be reintroduced by the action of ROMgBr (obtained from R·OH and a Grignard compound) in presence of Mg; cf. partial synthesis of chlorophyllide a from phaeophorbide a (*Fischer* and *Spielberger*, Ann. **510**, 156).

[3] Chlorophyll a can be degraded to this stage in the organism of the silk-worm (*Bombyx mori*) (*Fischer* and *Hendschel*, Z. physiol. Chem. **222**, 250).

(b analogous) (*Willstätter* and *Hocheder*, Ann. **354**, 205; *Fischer* and *Bäumler*, Ann. **474**, 69; *Fischer*, *Moldenhauer* and *Süs*, Ann. **486**, 156; *Fischer* and *Siebel*, Ann. **499**, 84; *Stoll* and *Wiedemann*, Helv. **16**, 183); with methyl alcoholic HCl the phytol residue is exchanged for methyl with the formation of methyl-phaeophorbide a, $C_{32}H_{32}ON_4(COOCH_3)_2$ (b analogous). The action of methyl alcoholic potash on the phaeophorbides hydrolyses off the methyl groups, and also sets free a further carboxyl group; in this way, chlorophyll a gives the olive-green tricarboxylic acid, phytochlorin e, $C_{34}H_{36}O_6N_4$ (trimethyl ester m.p. 263°), and chlorophyll b gives the red phytorhodin g, $C_{34}H_{34}O_7N_4$ (trimethyl ester m.p. 238°) (cf. *Fischer*, *Hendschel* and *Nüssler*, Ann. **506**, 83).

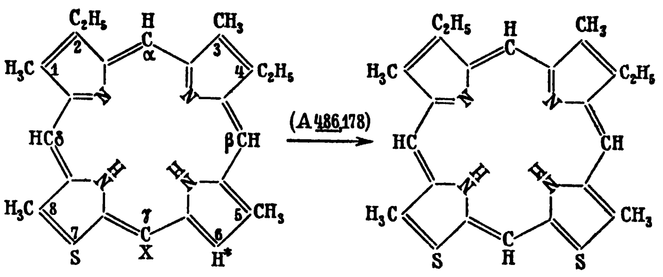
The oxidative degradation (*Willstatter* and *Asahina*, Ann. **373**, 227) and the reductive fission (idem, Ann. **385**, 188) of chlorophyll derivatives gave the first indication that the molecule was built up of pyrrole nuclei.

Further insight was obtained by investigating the *phyllins* and *porphyrins*, which are important compounds obtained by the energetic action of alkali ethoxide on chlorophyll at a high temperature. The constitution of these substances was elucidated by the fundamental work of *H. Fischer*, *A. Treibs* and their co-workers. In this reaction chlorophyll a yields:

Phylloporphyrin: $C_{32}H_{36}O_2N_4$ (previously $C_{31}H_{34}O_2N_4$),
Pyrroporphyrin: $C_{31}H_{34}O_2N_4$, two monocarboxylic acids,
Rhodoporphyrin: $C_{32}H_{34}O_4N_4$,
Verdoporphyrin: $C_{32}H_{32}O_4N_4$, dicarboxylic acids (*Treibs* and *Wiedemann*, Ann. 471, 146).

Phyllo- and pyrroporphyrin contain a free CH-group in one pyrrole nucleus of the porphin skeleton, since oxidation of the brominated porphyrins leads to bromocitraconimide (*Treibs* and *Wiedemann*, Ann. **466**, 278, 284). In rhodoporphyrin this free methine group is substituted by COOH; the decarboxylation of rhodoporphyrin to pyrroporphyrin is a conclusive proof of this close relationship. Phyllo- and pyrroporphyrin are converted by distillation with soda-lime into the oxygen-free phyllo-aetioporphyrin, $C_{31}H_{36}N_4$, m.p. 263°, and pyrro-aetioporphyrin, $C_{30}H_{34}N_4$, m.p. 284° (Cu salt m.p. 251°) (*Willstatter* and *Fischer*, Ann. **400**, 182; *Fischer* and *Treibs*, Ann. **466**, 188). Both of these substances have been synthesised (*Fischer* and *Helberger*, Ann. **480**, 235; *Fischer* and *Schormuller*, Ann. **473**, 211; *Fischer*, *Berg* and *Schormüller*, Ann. **480**, 109).

The determination of the constitution of pyrroporphyrin was of considerable importance in the next stage, since a knowledge of its skeleton gives the arrangement of the side-chains in the porphin nucleus of chlorophyll. This object was achieved essentially in two different directions: 1. by the general porphin synthesis of 1:3:5:8-tetramethyl-2:4-diethyl-porphin-7-propionic acid, which was identical with the pyrroporphyrin obtained from chlorophyll; and 2. by the introduction of a second propionic acid residue into the free methine group of pyrroporphyrin, which yielded the mesoporphyrin prepared from the blood pigment, haemin, i.e. 1:3:5:8-tetramethyl-2:4-diethyl-porphin-6:7-dipropionic acid (*Fischer* and *Riedl*, Ann. **486**, 178). By this means, *H. Fischer* and his school showed that the arrangement of the side-chains in the porphin skeleton of the porphyrins derived from chlorophyll (pyrro- and rhodoporphyrin) is the same as that in haemin, which is derived from aetioporphyrin III (see p. 458). The same holds true for phylloporphyrin, a homologue of pyrroporphyrin and easily converted into it by Na methoxide; the constitution of this has been shown by synthesis to be 1:3:5:8-tetramethyl-2:4-diethyl-γ-methyl-porphin-7-propionic acid (*Fischer* and *Helberger*, Ann. **470**, 235; *Fischer*, *Siedel* and *d'Ennequin*, Ann. **500**, 137).



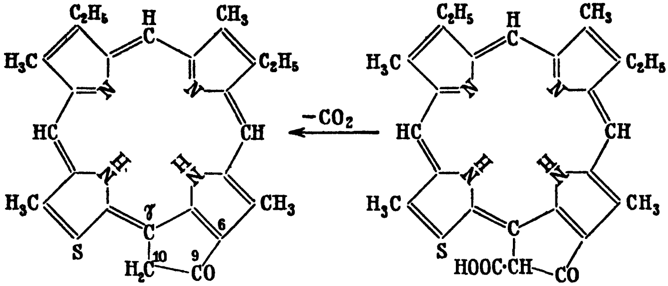
X = H: Pyrroporphyrin $C_{31}H_{34}O_2N_4$ (methyl ester m.p. 238°; synthesis Ann. **473**, 211; **480**, 109; **482**, 232).

X = CH_3: Phylloporphyrin $C_{32}H_{36}O_2N_4$ (methyl ester m.p. 230°; synthesis Ann. **480**, 235; **500**, 137).

* if in place of H, COOH Rhodoporphyrin $C_{32}H_{34}O_4$ (dimethyl ester m.p. 269°; synthesis Ann. **480**, 109).

Verdoporphyrin, $C_{32}H_{32}O_4N_4$ (dimethyl ester m.p. 280°, see *Treibs* and *Herrlein*, Ann. **506**, 1), contains two hydrogen atoms less than rhodoporphyrin.

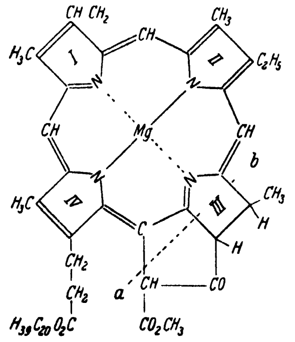
The degradation of chlorophyll by means of alkali ethoxide to these porphyrins is a very vigorous way of attacking the molecule, as is shown by the loss of carbon atoms which takes place. Consequently this method of settling the arrangement of the porphin nucleus and of the side-chains in the original substance is not entirely free from objection. It was at this stage that **phylloerythrin,** $C_{33}H_{34}O_3N_4$, a biological degradation product which had been known for a long time, gave considerable insight into the porphin skeleton upon which chlorophyll is based. Phylloerythrin is formed from chlorophyll in the third and fourth stomachs of ruminants (*Rothemund* and *Inman*, Am. **54**, 4702), and can be isolated from them or from the faeces (*Marchlewski*, Z. physiol. Chem. **43**, 464; *Goldmann*, *Hetper* and *Marchlewski*, ibid. **45**, 176), and alkali degradation in the presence of oxygen converts it, like chlorophyll, into a mixture of phyllo-, pyrro- and rhodo-porphyrins (*Fischer*, Ann. **502**, 187). By the action of HI-acetic acid, *Fischer* was able to obtain from chlorophyll artificially the so-called phaeoporphyrins, which are very similar in their spectra to phylloerythrin, and contain the porphin skeleton of chlorophyll essentially intact. For these reasons, phylloerythrin and the phaeoporphyrins were compounds of the greatest interest for further investigation. A fact which deserves special notice is that the most important of the phaeoporphyrins, known in the literature as phaeoporphyrin a_5, $C_{34}H_{34}O_5N_4$ (*Fischer* and *Süs*, Ann. **482**, 225; *Fischer*, *Moldenhauer* and *Sus*, Ann. **485**, 1; **486**, 107), can be decarboxylated to phylloerythrin, $C_{33}H_{34}O_3N_4$ (*Fischer*, *Filser*, *Hagert* and *Moldenhauer*, Ann. **490**, 1), which shows the close connection between the artificial and the biological degradation products (*Fischer* and *Riedmair*, Ann. **490**, 91; **499**, 288). The synthesis and properties of the phaeoporphyrins and of phylloerythrin (idem, ibid.) prove that an isocyclic five-membered ring containing a keto-group is an essential constituent of the porphin skeleton of chlorophyll; this ring unites C atom 6 (see pyrroporphyrin formula above) to the γ-methine C atom, by means of two carbon atoms in phylloerythrin, and by a branched chain of three carbon atoms in phaeoporphyrin a_5. Phaeoporphyrin a_5 and phylloerythrin are therefore represented by the following formulae:



Phylloerythrin Phaeoporphyrin a_5

The isocyclic ring is readily opened by hydrolysis; this reversible reaction leads to the chloroporphyrins, which are closely related to the haemin porphyrins in their absorption spectra. The action of 30% methyl alcoholic potash converts phaeoporphyrin partly into rhodoporphyrin (above), in which nothing remains of the isocyclic ring save the carboxyl group (see formula, p. 469).

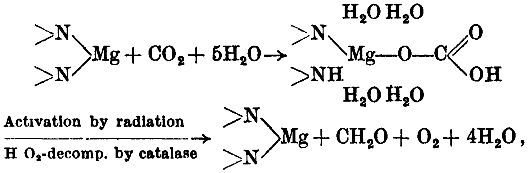
If phaeoporphyrin a_5 contains exactly the same porphin skeleton as natural chlorophyll, its known monomethyl ester must be identical with phaeophorbide (see p. 467). Actually, they show quite different absorption spectra; phaeoporphyrin a_5 has the typical two-banded spectrum of the porphyrins, while phaeophorbide has the multi-banded spectrum which is peculiar to chlorophyll (main band in the red). This discrepancy is due to the presence of a vinyl group, which can be detected with diazomethane, in ring I of the porphin skeleton of the original chlorophyll (*Fischer* and *Medick*, Ann. **517**, 245; *Fischer* and *Hasenkamp*, Ann. **519**, 42). This is shown in the following formula; the distribution of the alcohol residues on the two COOH groups, and the conversion of phaeoporphyrin a_5 monomethyl ester into phylloerythrin (cf. above), is in agreement with the known fact that carbomethoxy-groups attached to a secondary carbon atom are in general more difficult to hydrolyse (*Fischer* and *Kellermann*, Ann. **519**, 217; *Fischer* and *Stern*, Ann. **520**, 91). The only part of the formula which is in any doubt is below the line a b.



Chlorophyll b is one oxygen atom richer than the a-component; this O atom is probably present as a formyl group, and its formula is probably that shown above with CHO instead of CH_3 on nucleus II (*Fischer* and *Breitner*, Ann. **510**, 183; **511**, 183; **522**, 151).

Chlorophyll is the catalyst for the process which is fundamental in plant life, the synthesis of carbohydrates from water and carbon dioxide under the influence of sunlight (*Baeyer*, Ber. 3, 63).

Since experiment shows that the fundamental ratio $\frac{CO_2 \text{ absorbed}}{O_2 \text{ evolved}}$ is equal to unity (the so-called assimilatory coefficient: *Willstätter* and *Stoll*; Ber. **50**, 1777), the only theoretical possibility is that formaldehyde is the intermediate in this synthetic process, and this compound can, in fact, be detected with the aid of "dimedone" (see p. 112) or urea. The process of assimilation with the chlorophyll molecule can be represented, in a modified form of Willstätter's scheme, as follows (*R. Willstätter* and *A. Stoll*, Untersuchungen über die Assimilation der Kohlensäure, Springer, Berlin 1918; *K. Shibata*, Kohlenstoff- und Stickstoffassimilation, Iwanami, Tokyo 1931):



This is in agreement with energy considerations (see *Warburg* and *Negelein*, Z. physik. Chem. **106**, 191) which require the absorption of four light quanta for the reduction of the CO_2, and with the repression of the second, enzymatic portion of the process (and hence the separation of the oxygen) by poisoning the catalase with hydroxylamine (*Shibata* and *Yakushiji*, N. **21**, 267).

Oxygen is known to have the power of extinguishing the fluorescence, and hence must be regarded as the direct carrier of the light energy absorbed by the chlorophyll in assimilation (*Kautsky*, *Hirsch* and *Davidshöfer*, Ber. **65**, 1762). The easy dehydrogenation of chlorophyll indicates that it may have a function similar to that of glutathione (*Fischer*, *Süs* and *Klebs*, Ann. **490**, 38; *Fischer* and *Siebel*, Ann. **499**, 84).

Activated carbon dioxide acts as acceptor for the H atoms of the reduced stages of chlorophyll (*Stoll*, N. **20**, 955). For the possibility of the occurrence of a mono-dehydro-chlorophyll as an intermediate in the photo-reduction of carbon dioxide, see *Willstätter*, N. **21**, 252. For the reversible hydrogenation of chlorophylls to brown leucochlorophylls with Zn in pyridine, see *Kuhn* and *Winterstein*, Ber. **66**, 1741.

A certain amount of light is thrown on the question of the origin of technically important minerals, such as oil shale, asphalt, and the petroleum waxes and oils by the fact that there have been found in these minerals, even in those of the oldest geological formations, decomposition products of chlorophyll, such as desoxo-phylloerythrin, $C_{33}H_{36}O_2N_4$ (methyl ester, m.p. 264°), the synthetic intermediate of phylloerythrin, and desoxo-phylloerythro-aetioporphyrin, together with porphyrins which are derived from haemin. This fact seems to indicate that plants containing chlorophyll were partly responsible for the formation of bitumen and petroleum, and the preponderance of the chlorophyll porphyrins may indicate that they played the most important part (*Treibs*, Ann. **509**, 103; **510**, 42).

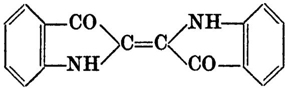
Bacterio-chlorophyll (bacteriochlorin). The sulphur-free purple bacteria contain a pigment which is closely related to chlorophyll, and probably has a photosynthetic function (*Noack* and *Schneider*, N. **21**, 835; *Schneider*,

Z. physiol. Chem. **226**, 221). It is derived from chlorophyll a (cf. formula p. 470) by replacement of the $CH_2{:}CH$ group on ring I by a $CH_3.CO$ group (*Fischer* and *Hasenkamp*, Ann. **515**, 148).

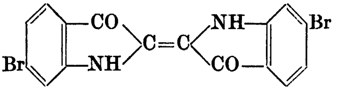
Indole Colouring Matters

Indigo (I), $C_{16}H_{10}O_2N_2$, which occurs as indican (the glucoside of indoxyl), $C_8H_6ON \cdot C_6H_{11}O_5$ (see p. 377), in *Indigofera tinctoria, Isatis tinctoria, Polygonum tinctorium,* etc., and also as the sulphonic acid, $C_8H_6ON \cdot SO_3H$, chiefly in the urine of herbivorous animals, is dealt with in vol. IV.

I



II

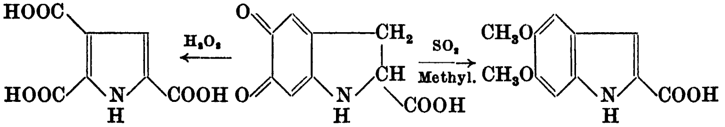


The **purple of the ancients** (6:6′-dibromo-indigo, II), $C_{16}H_8O_2N_2Br_2$, is formed by the action of light upon the glandular secretions of the shell-fish *Murex brandaris* (see *Friedländer*, Mo. **28**, 991). It can be synthesised by the following methods: from p-brom-anthranilic acid and chloracetic acid (idem, Ber. **42**, 765), by the oxidation of 6-brom-indole-3-carboxylic acid with ozone (*Majima* and *Kotake*, Ber. **63**, 2237), and by the condensation of 4-brom-2-nitro-benzaldehyde with acetone (*Rottig*, J. pr. **142**, 35).

Haliotis-indigo, the blue shell pigment of the shell-fish *Haliotis californiensis*, is allotted to the indigo series because of its absorption spectrum and its dyeing properties (*Schulz* and *Becker*, Biochem. Z. **236**, 99; *Lemberg*, Z. physiol. Chem. **200**, 173; *Schulz* and *Becker*, ibid. **203**, 157).

Hallachrome, $C_9H_7O_4N$, the red skin pigment of *Halla parthenopaea* (annelids), has been proved to be the 5:6-quinone of 2:3-dihydro-indole-2-carboxylic acid (I) (*Mazza* and *Stolfi*, Arch. Scienze biol. **16** (1931), 183). The compound, which is also observed as an intermediate in the formation of melanin (the so-called "red compound" of the tyrosinase-tyrosine reaction, see below), acts as an accelerator of respiration, corresponding to its character as a reversible biological oxidation-reduction system (*Stern*, N. **21**, 350; *Friedheim*, Biochem. Z. **259**, 275).

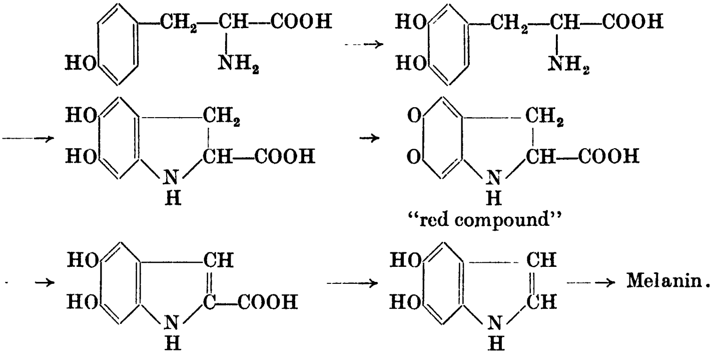
The distillation of the pigment with soda-lime in a stream of hydrogen yields pyrroline, giving at once an indication of the presence of a heterocyclic ring. Oxidation with H_2O_2 destroys the carbocyclic ring and gives pyrrole-2:4:5-tricarboxylic acid (II); treatment with sulphurous acid and methylation gives 5:6-dimethoxy-indole-2-carboxylic acid (III), $C_{11}H_{11}O_4N$, m.p. 202° (decomp.), and 5:6-dimethoxy-indole, $C_{10}H_{11}O_2N$:



(II) (I) (III)

The **melanins** are widely distributed in nature. The colour of the hair (*Tadokoro* and *Ugami*, J. Biochem. **12** (1930), 187), of the skin (*Connor*, Amer. J. Pathol. **4** (1928), 293) and of the eyes (*Waelsch*, Z. physiol. Chem. **218**, 35) of the higher animals is due to the presence of such pigments. They also occur in the so-called melanotic tumours (*Adler*, Biochem. Z. **217**, 324) and in the urine (*Medes* and *Berglund*, Proc. Soc. Exp. Biol. Med. **25** (1928), 635); the pigments which appear under pathological conditions, in the so-called human ochronosis, are also melanins (*Fink*, Z. physiol. Chem. **197**, 193, note 1). The colour of the cocoons of the chrysalis of several butterflies and leafwasps is due to melanin (*Przibram*, C. 1925 I 2092). It is also found in cultures of *Azotobacter chroococcum*, etc. (*Rippel* and *Ludwig*, Zentr. Bakt. **64** (1925), II, 161; *Lloyd* and *Johnston*, J. Roy. Tech. Coll. **2**, (1930), 346), and in many plants, such as the broom, the broad bean and the horse-chestnut, and in fruits (*Schmalfuss* and *Barthmeyer*, Biochem. Z. **190**, 424). The dark colour which develops in potatoes by the natural death of the cells, and on freezing or heating and by the action of narcotics or infections, is due to the appearance of melanins (*Boas* and *Merkenschlager*, Biochem. Z. **155**, 197).

The formation of melanin in animal and plant organisms has its origin in the enzymatic oxidation of the tyrosine of the protein by tyrosinase (*Schmalfuss*, N. **15**, 453; *Raper*, Biochem. J. **21** (1927), 89; *Bloch*, Amer. J. Med. Sci. **177**, 609; *Friedheim*, N. **21**, 177), and it takes place with the intermediate formation of the "red compound" (see above, hallachrome):



Tyramine (*Dulière* and *Raper*, Biochem. J. **24** (1930), 239) and adrenalin (*Stefl*, C. r. Soc. Biol. **108** (1931), 985; *Heard* and *Raper*, Biochem. J. **27** (1933), 36) can also serve as starting materials for the biochemical synthesis of melanin.

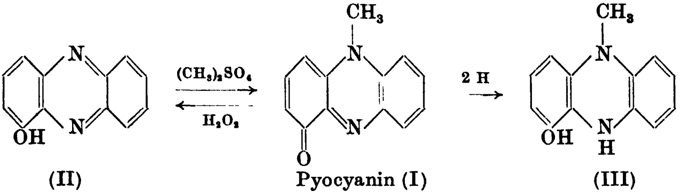
The following is a summary of the experimental facts upon which this scheme of reactions is based. When tyrosine is irradiated in the presence of oxygen with light of wave-length 320–310 $m\mu$, which lies in its absorption region, it turns deep brown and loses one molecule of CO_2. It is this same region of the spectrum which has such a characteristic action on the skin (*Friedheim*, N. **21**, 177). The formation of melanin from tyrosine and tryptophan by boiling them with sugar and HCl is hindered by stannous chloride (*Norita*, Bull. Agri. Chem. Soc. Japan **6** (1930), 23). Introduction of methyl groups into the ring of an aromatic amino-acid also checks the formation of the pigment (*Schmalfuss* and *Peschke*, Ber. **62**, 2591). In fishes, indole, skatole, α-methylindole and tyrosine increase the formation of dark pigments (*Comini*, Arch. di Fisiol. **23** (1925), 247). Subcutaneous injection of adrenalin-black causes melanodermia and melanuria (*Saccardi*, Lincei (6) **9** (1929), 1114). Ultra-violet light and X-rays accelerate the synthesis of the pigment (*Hance*, Science **66** (1927), 353; *Lignac*, C. 1930 I 1821).

Naturally occurring

Phenazine Colouring Matters

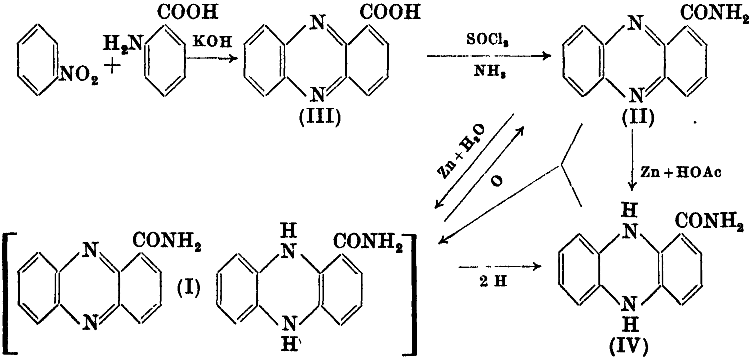
have been found so far only in bacteria.

Pyocyanin, $C_{13}H_{10}ON_2$ (*picrate* decomp. 190°), is the blue pigment of *Bacillus pyocyaneus*. Oxidation with H_2O_2 yields formic acid and 1-hydroxy-phenazine (II), $C_{12}H_8ON_2$, m.p. 158°, and the latter is also obtained, together with methyl iodide, by *Zeisel's* method (*Wrede* and *Strack*, Z. physiol. Chem. **140**, 1; **142**, 103; **181**, 58). Catalytic hydrogenation gives 1-hydroxy-N-methyldihydro-phenazine (III). Pyocyanin has been synthesised by methylating 1-hydroxy-phenazine (idem. ibid. **177**, 177; **181**, 74; Ber. **62**, 2051). These facts led to the view that the pyocyanin molecule is made up of two molecules of 1-hydroxy-N-methyl-dihydrophenazine united together with the loss of 4 H (*Wrede* and *Strack*, Z. physiol. Chem. **140**, 1; **142**, 103; **181**, 58). It is, however, impossible to construct a formula for such a compound which does not contravene the usual valency rules for the elements, and potentiometric titration shows that the pyocyanin molecule is an oxidation product of only one molecule of the dihydrophenazine (*Friedheim* and *Michaelis*, J. Biol. Chem. **91** (1931), 355; *Elema*, Rec. **50**, 807; *Michaelis* and *Holl*, Am. **55**, 1492). Hence pyocyanin is the quinonoid compound (I) derived from the dihydrophenazine by the loss of 2 H.



In the bacterial organism, pyocyanin acts as a respiratory enzyme, for it can cause the conversion of oxyhaemoglobin and haemoglobin into methaeglobin (*Stern*, N. **21**, 350). It also accelerates the respiration of the colourless bacteria, and acts in a non-specific manner (*Friedheim*, J. exp. Med. **54** (1931), 207).

Chlororaphin, (I), $C_{26}H_{20}O_2N_6$, m.p. 225–230° decomp., the green metabolism product of *Bacillus chlororaphis*, has been shown to be a quinhydrone-like compound of phenazine-α-carboxylic amide (II) and its dihydro-compound (IV). Atmospheric oxidation of the pigment leads to the yellow oxy-chlororaphin (II), $C_{13}H_9ON_3$, m.p. 241°, which has been identified by its hydrolysis to ammonia and phenazine-α-carboxylic acid (III), $C_{13}H_8O_2N_2$, m.p. 237°, and by its synthesis (see below). Chlororaphin and oxy-chlororaphin are converted by reduction into the orange-yellow dihydro-phenazine α-carboxylic amide (IV), $C_{13}H_{11}ON_3$, m.p. 194°. The complete synthesis of chlororaphin from nitrobenzene and anthranilic acid is carried out as follows (*Kögl* and *Postowsky*, Ann. **480**, 280):



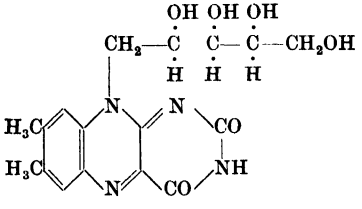
The quinhydrone structure of the pigment is established beyond doubt by its partial synthesis from the two components (II) and (IV); (see *Kögl* and *Tönnis*, Ann. **497**, 265; *Clemo* and *McIlwain*, J. **1935**, 738).

Violacein, $C_{42}H_{35}O_6N_5$, a violet dyestuff, decomp. > 350° (*acetate*, red-brown needles, decomp. > 300°), is obtained from *Chromobacterium violaceum* (*Kögl* and *Tönnis*, Ann. **265**, 275; *Wrede* and *Rothhaas*, Z. physiol. Chem. **223**, 113).

Alloxazine Colouring Matters

The **lyochromes** or **flavins** are yellow to yellowish-red pigments with a strong yellowish-green fluorescence, which are found in animal organs and products, such as liver ("hepaflavin", $C_{17}H_{20}O_6N_4$, m.p. 280°, *Stern*, Z. physiol. Chem. **212**, 207; Ber. **66**, 555; *Karrer*, *Salomon* and *Schöpp*, Helv. **17**, 419), heart, kidney, muscle ("cytoflavin" see *Banga* and *Szent-Györgyi*, Biochem. Z. **246**, 203), tumours (*Bierich*, *Lang* and *Rosenbohm*, N. **21**, 496), brain, eye, *corpus luteum* (*v. Euler* and *Adler*, Z. physiol. Chem. **223**, 105), and also have been obtained from hens' eggs ("ovoflavin", $C_{17}H_{20}O_6N_4$, decomp. 267°, see *Kuhn*, *György* and *Wagner-Jauregg*, Ber. **66**, 576), whey ("lactoflavin", $C_{17}H_{20}O_6N_4$, m.p. 292° (decomp.), see p. 572), urine ("uroflavin", m.p. 272° (decomp.), see *Stern* and *Greville*, N. **21**, 720; *Koschara*, Ber. **67**, 761), and the cerebrospinal fluid (*Gyorgy* and *Kuhn*, N. **21**, 405); they occur further in plants, such as spinach, tomatoes, etc., and in yeast and various bacteria. They are isolated by adsorption on fullers' earth, lead sulphide, etc., followed by elution with pyridine (*Ellinger* and *Koschara*, Ber. **66**, 315; *Kuhn*, *György* and *Wagner-Jauregg*, ibid. 317). They are closely related to the second respiratory ferment which is insensitive to CO and HCN and has been isolated by *Warburg* from blood and yeast (abs. max. 470, 445 mμ, see *Warburg* and *Christian*, Biochem. Z. **242**, 206; **254**, 438; **257**, 492; **258**, 496; N. **20**, 688, 980). In their composition (20 — 30% N) and in optical behaviour (abs. max. of the pigment from ox-heart 242, 267, 445 mμ; from liver 538, 562, 437 mμ; from egg albumen 267, 360, 433, 446 mμ), they are very like the butterfly pigments (pterins, see below; e.g. xanthopterin, abs. max. 243, 267, 360, 391 mμ, see *Wieland* and *Schöpf*, Ber. **58**, 2178; **59**, 2067), and alloxazine (abs. max. 260, 330, 425 mμ, see *Kuhn* and *Bär*, Ber. **67**, 898).

The constitution of lactoflavin, a compound of great physiological importance because it is vitamin B_2 and also a component of the yellow respiratory ferment, has been established as 6:7-dimethyl-9-d-ribityl-isoalloxazine (see p. 574):



The flavins from the various sources mentioned above are very similar to lactoflavin, and perhaps are identical with it.

The flavins also occur in nature in a non-dialysable form, as flavoproteins, combined with compounds of high molecular weight, e.g. in the liver, and in yeast (*Warburg* and *Christian*, Biochem. Z. **266**, 377; *György*, *Kuhn* and *Wagner-Jauregg*, Z. physiol. Chem. **223**, 241; see Vitamins, p. 571).

The pigments, which are soluble in water and dialysable, but insoluble in indifferent organic solvents, and are sensitive to light and alkali, are characterised by vitamin B_2 activity (see Vitamins, p. 572). Their amphoteric nature is shown by the formation of Pb, Ag and Tl salts, and by the variation of their fluorescence with pH (*Kuhn* and *Moruzzi*, Ber. **67**, 888). The pigments, which are stable to oxidising agents, can be reduced by hydrosulphites, catalytic hydrogenation with Pd, Zn or Na amalgam in acid solution to their leuco-compounds, via an unstable red intermediate (*Kuhn* and *Wagner-Jauregg*, Ber. **67**, 361; cf. the similar behaviour of alloxazine, *Kuhn* and *Bär*, ibid. 898); the pigment can be regenerated from the leuco-compound by shaking with air, or with bromine water or with methylene blue, and these properties make it behave like a natural redox system (*Bierich, Lang* and *Rosenbohm*, N. **21**, 496; *Wagner-Jauregg* and *Ruska*, Ber. **66**, 1298; *Kuhn, Rudy* and *Wagner-Jauregg*, ibid. 1950; *Kuhn* and *Wagner-Jauregg*, Ber. **67**, 361). Flavins increase the respiration of bacteria (*Adler* and *v. Euler*, Z. physiol. Chem. **225**, 41), of erythrocytes (*Stern* and *Greville*, N. **21**, 720) and of the cell-tissue of higher animals.

Purine Colouring Matters

The **pterins** include the pigments of various butterflies, wasps, etc.

The wings of the cabbage white (*Pieris brassicae* etc.) and the white parts of the wings of the orange-tip butterfly contain the colourless **leucopterin**, $C_{19}H_{19}O_{11}N_{15}$, m.p. $> 400^0$. The pigment, which can be obtained crystalline by repeated precipitation from alkaline solution with mineral acids, behaves on titration as a tetrabasic acid, and gives a crystalline acid disodium salt which is yellow. With conc. H_2SO_4 rearrangement takes place to *iso-leucopterin*, which behaves as a hexabasic acid.

Leucopterin shows the murexide reaction, and reacts with phosphotungstic acid. It gives a trichlor-derivative with PCl_5—$POCl_3$, and a triglycol (or a hexamethyl ether) when oxidised with Cl_2 in water (or in methyl alcohol). It also forms a triacetyl compound. All these facts seemed to indicate that its structure is based on uric acid (*Schöpf* and *Wieland*, Ber. **59**, 2067). Such a view is, however, excluded by the facts that guanidine has been found among the decomposition products of various leucopterin derivatives, and that oxidation of leucopterin with HNO_3 gives none of the typical oxidation products of uric acid, such as alloxan and allantoin. Treatment of leucopterin with nitrite and conc. H_2SO_4 gives desimino-leucopterin, $C_{19}H_{14}O_{13}N_{12}$, three N atoms being lost, and complete hydrolysis of this compound gives no guanidine (cf. the conversion of guanine into xanthine). With conc. HCl at 170^0, leucopterin gives glycine, ammonia and CO_2, which are typical uric acid products, also CO, and hydrolysis of leucopterin-triglycol $C_{19}H_{19}O_{11}N_{15}(OH)_6$ gives, in contrast to uric acid, oxalic acid together with guanidine, NH_3 and CO_2. Decomposition of leucopterin-triglycol-hexamethyl ether, $C_{19}H_{19}O_{11}N_{15}(OMe)_6$ gives guanidine and CO_2 and an important degradation product, an acid $C_4H_5O_4N_2(OMe)$ m.p. 182^0, which can be given the constitution

$$H_2N \cdot CO \cdot CH(OMe) \cdot NH \cdot CO \cdot CO_2H,$$

and can be hydrolysed to glyoxylic acid or oxalic acid.

Quantitative investigation of these decompositions of the leucopterin molecule suggest a complex formula made up of three imino-purine or pyrimidine nuclei joined by the C-atoms of the oxalic acid, or its decomposition products, CO_2 and CO; two of the heterocyclic units seem to behave alike, as is shown by the formation of a diglycol, $C_{19}H_{25}O_{16}N_{15}$, with chlorine in acetic acid, by the presence of only two mol. of guanidine in the hydrolysis products of the triglycol, and the formation of one mol. of guanidine in the degradation of the triglycol trimethyl ether, $C_{19}H_{19}O_{11}N_{15}(OH)_3(OCH_3)_3$.

Formulae for this complex natural product, which will explain these interesting results, have been suggested by *Wieland* and *Schöpf* (Ann. **507**, 226).

Xanthopterin, $C_{19}H_{19}O_7N_{15}$, m.p. $> 400^0$, the yellow wing pigment of the brimstone butterfly (*Gonopterix rhamni*), can also be obtained from wasps and hornets and shows an amphoteric character like leucopterin (yellow Ba salt monohydrate, $C_{19}H_{15}O_8N_{15}Ba_3$; colourless hydrochloride); it evolves ammonia when boiled with alkali. It couples with diazo-compounds (cf.

xanthine), and gives the murexide test and can be oxidised to uric acid. These facts show that it is closely related to leucopterin (*Wieland* and *Schöpf*, Ber. **58**, 2178; *Schöpf* and *Becker*, Ann. **507**, 266).

The older idea that free uric acid was present in the wings of butterflies has not been confirmed by more recent investigation.

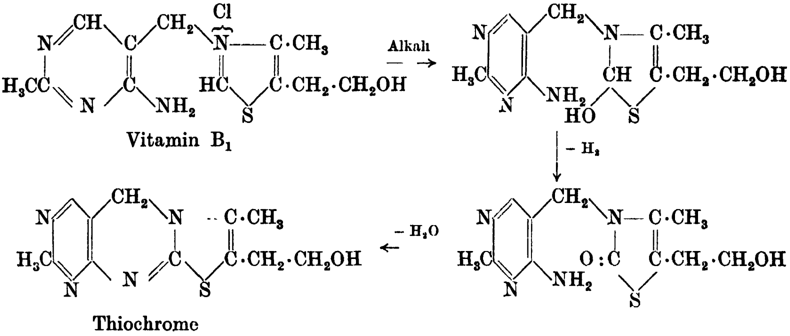
A complex system of condensed heterocyclic rings is present in the colouring matter

Thiochrome, $C_{12}H_{14}ON_4S$, m.p. 228° (corr.) (hydrochloride m.p. 217–221°), which has a strong blue fluorescence in solution. It was first isolated by *Kuhn* and his co-workers from yeast: 4,050 kg. of yeast yielded 250 mg. of thiochrome (Z. physiol. Chem. **234**, 196). It is soluble in water and methyl alcohol, but difficultly soluble in acetone, chloroform and ether. With reducing agents ($Na_2S_2O_4$ or catalytic hydrogenation), two mol. of hydrogen are taken up with the formation of a leuco-compound, which is readily re-oxidised by oxygen.

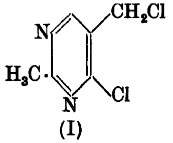
The same compound was obtained by *Barger*, *Bergel* and *Todd* (Nature **136**, 259; Ber. **68**, 2257) by oxidation of an alkaline solution of vitamin B_1 (p. 569) (aneurin) with ferricyanide. This relation between thiochrome and aneurin is shown by their formulae;

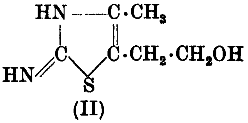
Vitamin B_1 (chloride-hydrochloride); $C_{12}H_{17}ON_4SCl \cdot HCl$
Thiochrome; $C_{12}H_{14}ON_4S$

When the structure of the vitamin had been established, that of thiochrome was a natural consequence (*Windaus*, *Tschesche* and *Grewe*, Z. physiol. Ch. **237**, 98; *Grewe*, ibid. **242**, 93; *Todd* and *Bergel*, J. **1936**, 1559):



This structure has been confirmed by the synthesis of thiochrome, by condensing 4-chloro-5-chloromethyl-2-methylpyrimidine (I) with 2-amino-4-methyl-5-β-hydroxyethylthiazole (II) (*Todd*, *Bergel*, *Fraenkel-Conrat* and *Jacob*, J. **1936**, 1601).


(I)


(II)

NITROGEN-FREE (NON-ALKALOIDAL) POISONS

Poisonous compounds of the plant and animal kingdom, with the exception of amines, alkaloids and other nitrogenous substances (such as mustard oils, see p. 367; HCN glycosides, see p. 364), are dealt with in this section, and they are arranged according to their chemical constitutions, as far as these are known.

The poisonous action is frequently associated with the presence of an unsaturated lactone group in the molecule, but the physiological action is specifically influenced by the constitution of the molecule as a whole.

With the exception of a few aliphatic substances, such as jalapic acid, convolvulinic acid, agaricic acid and the fatty acids of the tubercle bacillus, these poisons are almost entirely cyclic substances. Thus anemonin is a cyclobutane derivative; the insect poisons hydnocarpic acid, chaulmoogric acid and the pyrethrins are derivatives of cyclopentane. The hydroaromatic compounds include picrocrocin, sedanolide and cantharidin, the blistering substance of the Spanish fly. Alantolactone, santonin, picrotoxin and the podophyllins are unsaturated lactones of the hydronaphthalene series. Derivatives of the aromatic series with specific physiological action include the alkylated pyrocatechols, urushiol, laccol and thitsiol, which cause violent skin inflammation, the anthelmintics of the fern, such as filicic acid, etc., several quinones, which have a strong irritant effect upon the respiratory passages, and the polyhydroxy-anthraquinones which have been used as purgatives, etc. Finally, there are the derivatives of coumarin which act as strong fish poisons, such as bergapten, peucedanin, etc., and the benzo-γ-pyranone derivatives, rotenone, deguelin, tephrosin and toxicarol; cannabinol, the intoxicating poison of hashish from Indian hemp, also belongs to this series. The large class of the saponins, of which the most important therapeutically is the *Digitalis* group, is distinguished by haemolytic properties and cardiac action; these contain the same complex hydro-aromatic system as the bile acids, and the toad and snake poisons, which have a similar physiological effect.

(a) FATTY ACIDS

Jalapic acid, $C_{34}H_{62}O_{18}$, m.p. 208°, prepared from the resins of *Jalape convolvulus* and *Scammonia*, is a compound of *jalapinolic acid,* $C_{16}H_{32}O_3$, m.p. 63° (11-hydroxy-palmitic acid), and three mol. of glucose (cf. p. 353). It causes haemolysis (*Heinrich*, Biochem. Z. 88, 13), and paralysis of the parasympathetic system and of the motor nerves. and, in the form of powdered jalap, has been used as a purgative.

Convolvulinic acid, $C_{52}H_{92}O_{32}$, m.p. 187°, which likewise occurs in various species of *Convolvulus,* is similar to jalapic acid in its physiological action and has a very marked purgative action; it can be hydrolysed to *convolvulinolic acid,* $C_{16}H_{32}O_4$, m.p. 84° (3:12-dihydroxy-palmitic acid), four mol. of glucose and two mol. of rhamnose (see p. 354).

The larch fungi, *Polyporus off.* and *Fomes off.*, contain **agaricic acid,** $C_{22}H_{40}O_7$, m.p. 142° (trimethyl ester m.p. 64°). In addition to its haemolytic properties it has an effect on the heart (*Ransom*, J. Physiol. **51** (1917), 176; *McCartney* and *Ransom*, ibid. 287; *McCartney*, J. pharm. Exp. Ther. **10** (1917), 83), and has been shown to decrease perspiration (*Schön*, C. 1923 III 962). For its constitution, see p. 381.

The lipoids of the tubercle bacillus contain fatty acids with branched chains: **tuberculo-stearic acid,** $C_{18}H_{36}O_2$, an oil, b.p. 142—149°/ 0·001 mm., and **phthionic acid,** $C_{26}H_{52}O_2$, m.p. 28°, which are combined with sugar and alcohols of high molecular weight (*Andersson* and

Chargaff, J. Biol. Chem. 85 (1929), 77; *Chargaff*, Ber. **65**, 745; *Andersson* and *Chargaff*, Z. physiol. Chem. **191**, 157; *Chargaff*, N. **19**, 202). By fractionation of its methyl ester, b.p. 190—198°/0·001 mm. in a high vacuum, the latter can be separated into two optical isomers, $[\alpha]_D + 10{\cdot}5°$ and $[\alpha]_D - 5°$ (*Andersson*, C. 1932 II 3429). The sodium salt of the former acid acts upon *Mycobact. leprae*, the latter is an antigen and causes giant-cell growth (*Sabin*, *Doan* and *Forkner*, J. Exp. Med. 52 (1930), suppl. 3, 3). For the synthesis of fatty acids with branched chains, see *Chargaff*, Ber. **65**, 745.

(b) REDUCED CARBOCYCLIC COMPOUNDS

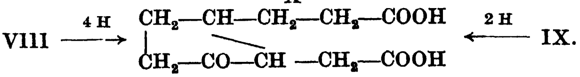
Cyclobutane Derivatives

Anemonin (I, p. 480), $C_{10}H_8O_4$, m.p. 158° (decomp.), is obtained by steam distillation of the crude oil from various species of *Anemone* and *Ranunculus* (*Meyer*, Mo. **17**, 283); it is not originally present as such, but is formed during the distillation by the polymerisation to a 4-ring of dehydro-α-angelica-lactone, which occurs in these plants (cf. synthesis, p. 481). It paralyses respiration and the beating of the heart (*Raymond-Hamet*, C. 1927 II 121; *Asahina*, Ber. **47**, 914) and produces inflammation (*Asahina* and *Fujita*, Acta phytochim. **1** (1922), 1).

Anemonin contains two olefinic double bonds (tetrabromide $C_{10}H_8O_4Br_4$, m.p. 175°, see *Asahina*, Ber. **47**, 914) which can be reduced with Pt and H_2 to give tetrahydro-anemonin (II), $C_{10}H_{12}O_4$, m.p. 156° (*Asahina*, Arch. Pharm. **253** (1915), 590; *Asahina* and *Fujita*, J. Pharm. Soc. Japan **1921**, no. 70, 1). Na amalgam and acetic acid only open the four-membered ring and give the dihydro-compound (III), $C_{10}H_{10}O_4$, m.p. 172°, while Na and alcohol give iso-tetrahydroanemonin (IV), $C_{10}H_{12}O_4$, m.p. 142°, a derivative of cyclohexane. The four O atoms of anemonin are present in two lactone groups (*Meyer*, Mo. **20**, 634); thus dihydro-anemonin with conc. HCl gives anemonolic acid (V), $C_{10}H_{14}O_6$, m.p. 158° (dimethyl ester m.p. 95°), and the sodium salt of tetrahydro-anemonin (VI), $C_{10}H_{14}O_6Na_2$, is formed by alkaline hydrolysis of tetrahydro-anemonin. With anemonin itself aqueous potassium carbonate hydrolyses the lactone groups and also opens the cyclobutane ring, giving α-anemoninic acid (VII), $C_{10}H_{12}O_6$, m.p. 117° (which rearranges with HCl into the β-form, m.p. 189°); with sodium ethoxide it yields α-anemonic acid (VIII), $C_{10}H_{10}O_5$, m.p. 120°, (which rearranges with HCl to the β-form, m.p. 208°), a 5-ring being formed.

The transition from the cyclobutane series (anemonin) to the cyclopentane series (anemonic acid) also takes place in the reactions: anemonin → dihydro-anemonin → anemonolic acid → anhydro-anemonolic acid (IX), $C_{10}H_{12}O_5$, m.p. 129°. Anemonic acid and anhydro-anemonolic acid take up two and four atoms of H on catalytic hydrogenation to form tetrahydro-anemonic acid (X), $C_{10}H_{14}O_5$, m.p. 135° (dihydro-anhydro-anemonolic acid):

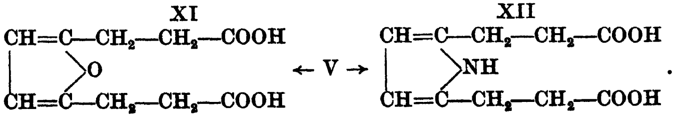
X



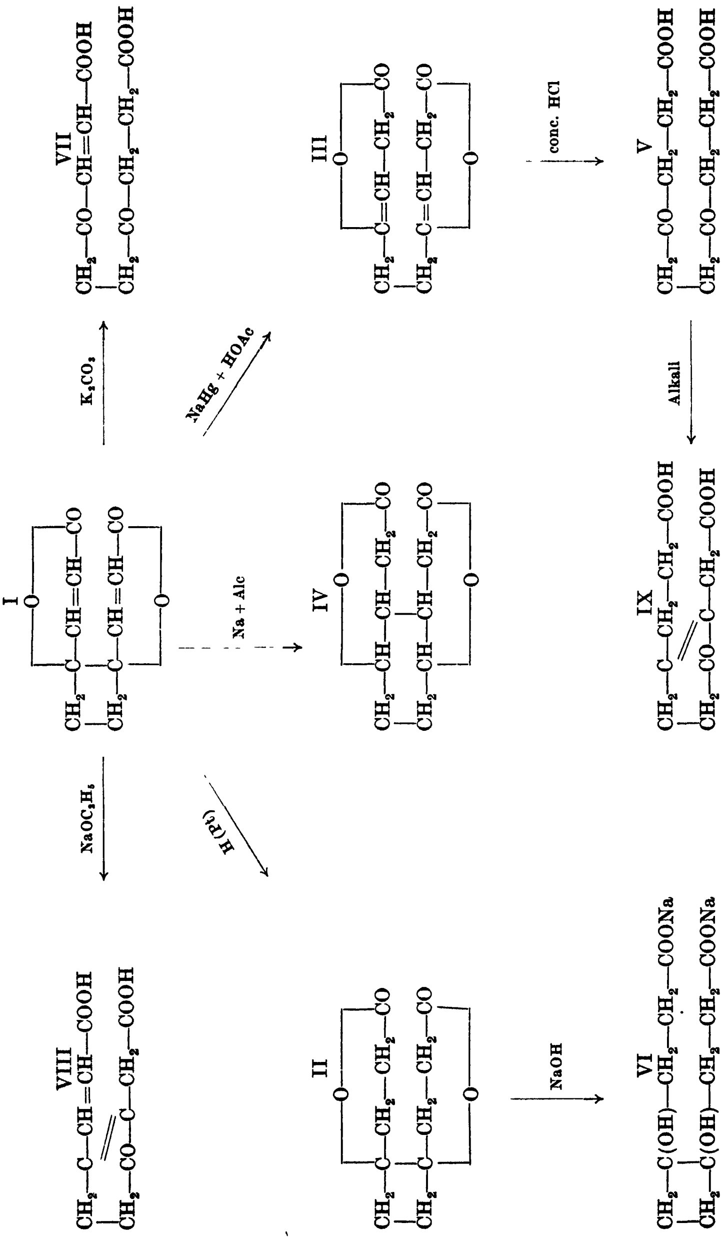
$$\mathrm{VIII} \xrightarrow{4\,H} \begin{array}{l} \mathrm{CH_2—CH—CH_2—CH_2—COOH} \\ | \\ \mathrm{CH_2—CO—CH\ —CH_2—COOH} \end{array} \xleftarrow{2\,H} \mathrm{IX}.$$

As a 1:4-diketo-compound, anemonolic acid when heated alone is converted into *furan-αα′-dipropionic acid* (XI), $C_{10}H_{12}O_5$, m.p. 154°; when heated with ammonia, it gives *pyrrole-αα′-dipropionic acid* (XII), $C_{10}H_{13}O_4N$, m.p. 170°:

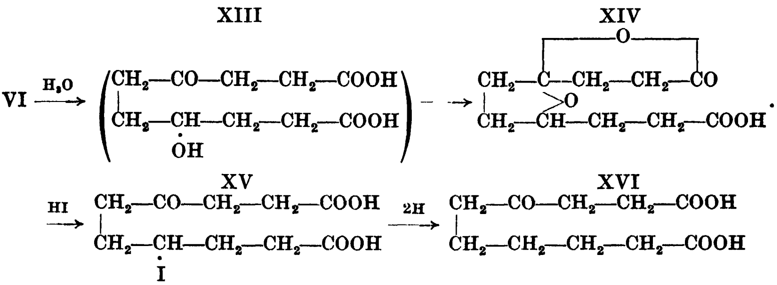
XI XII



$$\begin{array}{l} \mathrm{CH{=}C—CH_2—CH_2—COOH} \\ |\quad\ \ \rangle \mathrm{O} \\ \mathrm{CH{=}C—CH_2—CH_2—COOH} \end{array} \leftarrow \mathrm{V} \rightarrow \begin{array}{l} \mathrm{CH{=}C—CH_2—CH_2—COOH} \\ |\quad\ \ \rangle \mathrm{NH} \\ \mathrm{CH{=}C—CH_2—CH_2—COOH} \end{array}.$$

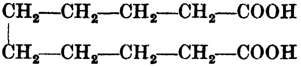

VIII
I
VII
K₂CO₃
NaOC₂H₅
Na + Alc
H(Pt)
NaHg + HOAc
II
IV
III
NaOH
conc. HCl
VI
IX
V
Alkali

When the Na salt of tetrahydro-anemonin is heated with water, an intermediate compound (XIII) is first formed, and then the hydrofuran-compound ψ-tetrahydroanemonic acid (XIV), $C_{10}H_{14}O_5$, m.p. 113°; this can be converted into the iodo-compound (XV), $C_{10}H_{15}O_5I$, m.p. 124°, which can be reduced with Zn and HCl to acetone-acetic-valeric acid (XVI), $C_{10}H_{16}O_5$, m.p. 90°:


XIII XIV XV XVI

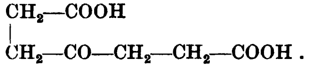
Further reduction of both dihydro-anemonin and acetone-acetic-valeric acid gives sebacic acid (XVII), $C_{10}H_{18}O_4$, m.p. 133°. Oxidation of anemoninic acid leads to acetone-diacetic acid (XVIII), $C_6H_{10}O_5$, m.p. 142° (*Asahina* and *Fujita*, Acta Phytochim. **1** (1922), 1):

XVII



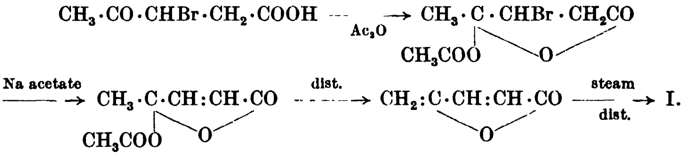
$$\begin{array}{l} CH_2{-}CH_2{-}CH_2{-}CH_2{-}COOH \\ | \\ CH_2{-}CH_2{-}CH_2{-}CH_2{-}COOH \end{array}$$

XVIII



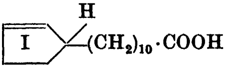
$$\begin{array}{l} CH_2{-}COOH \\ | \\ CH_2{-}CO{-}CH_2{-}CH_2{-}COOH\,. \end{array}$$

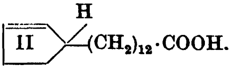
Anemonin has been synthesised as follows: β-bromolaevulinic acid was converted via acetyl-bromo-laevulinic acid and acetyl-acetacrylic acid lactone into dehydro-α-angelica-lactone (proto-anemonin), which on steam distillation polymerised to anemonin (idem, ibid.):



Cyclopentane Derivatives

The seeds of the tree *Hydnocarpus alcalae*, which grows in the Philippines, yield chaulmoogra oil; this contains **hydnocarpic acid** (I), $C_{16}H_{28}O_2$, m.p. 60°, $[\alpha]_D + 68{\cdot}3°$, amide m.p. 112° (*Perkins, Cruz* and *Reyes*, Ind. Eng. Chem. **19** (1927), 939) and the homologous **chaulmoogric acid** (II) (gynocardic acid), $C_{18}H_{32}O_2$, m.p. 68·5°, $[\alpha]_D + 62{\cdot}4°$, amide m.p. 107° (*Dean* and *Wrenshall*, Am. **42**, 2626; *André* and *Jouatte*, Bull. **43** (1928), 347):

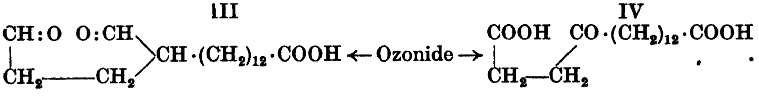




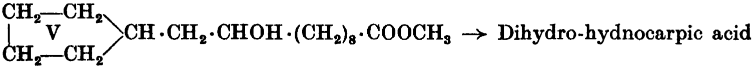
The acids are haemolytic (*Read*, J. Pharm. Exp. Ther. **24** (1924), 221), and also have a bactericidal action on *Mycobact. leprae* (*Stanley* and *Adams*, Am. **54**, 1548), and hence the oil has been long used in the East as a native remedy for leprosy and tuberculosis (*Walker* and *Sweeney*, J. Infect. Dis. **26** (1920), 238; *Wade*, Philippine J. Sci. **26** (1924), 21; *Perrot*, Boll. chim.

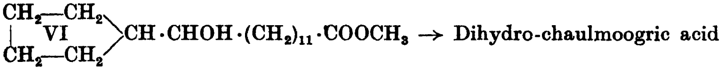
farm. **66** (1927), 610). The acids also act as fish and insect poisons (*Kendall*, French Pat. 247,242, 603,552; *Perrot*, loc. cit.).

Catalytic reduction gives the corresponding dihydro-compounds, m.p. 65° and 72° (*Shriner* and *Adams*, Am. 47, 2727). Reduction of the ozonide of chaulmoogric acid with Zn and acetic acid gives αγ-dialdehydo-n-pentadecane-α′-carboxylic acid (III), $C_{18}H_{32}O_4$ (a glass), which is converted by CrO_3 into n-pentadecane-αγα′-tricarboxylic acid (trimethyl ester m.p. 38°); further oxidation of the ozonide with permanganate leads to γ-keto-n-pentadecane-αα′-dicarboxylic acid (IV), $C_{17}H_{30}O_5$, m.p. 126°, which is reduced by Clemmensen's method to n-pentadecane-dicarboxylic acid, m.p. 118° (idem, ibid.; *Perkins*, Am. 48, 1714):

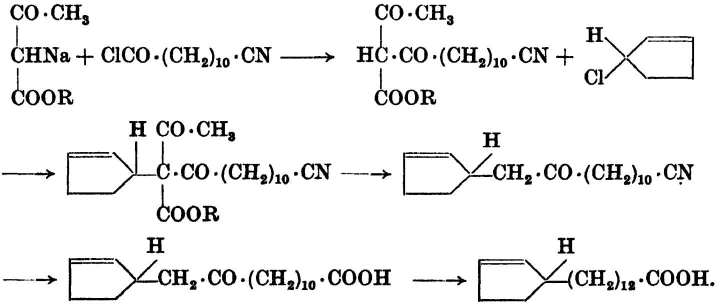


The constitutions of both cyclic fatty-acids have been proved by synthesis of their dihydro-compounds: the Grignard compound of chlormethyl-cyclopentane was condensed with ω-formyl-nonanoic methyl ester to give the hydroxy-ester (V), which was converted, via the bromide, into dihydro-hydnocarpic acid. In a similar way, dihydro-chaulmoogric acid has been prepared from cyclopentyl-magnesium bromide and ω-formyl-dodecanoic methyl ester, via the hydroxy-ester (VI) (*Noller* and *Adams*, Am. 48, 1080):



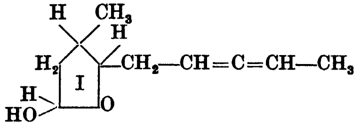


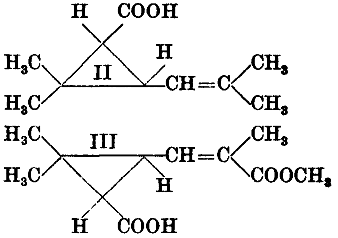
A partial synthesis of chaulmoogric acid has been carried out from hydnocarpic acid and malonic ester (*Stanley* and *Adams*, Am. 51, 150). The complete synthesis of chaulmoogric acid has been achieved thus: the condensation product of 11-cyano-undecanoic acid chloride and sodio-acetoacetic ester was allowed to react with Δ^2-chlorcyclopentene; after ketonic hydrolysis, the cyano-group was hydrolysed and the resulting keto-acid reduced by the Kishner-Wolff method (*Perkins* and *Cruz*, Am. 49, 1070):



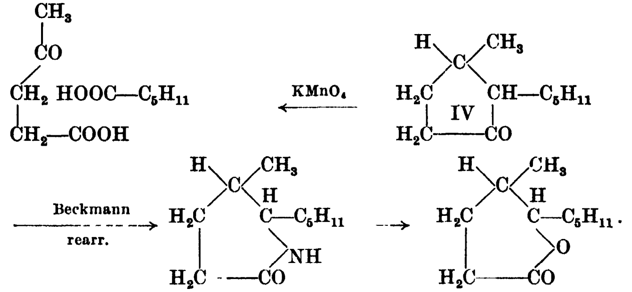
The **pyrethrins** I and II, the insect poisons from the flowers of the Dalmatian composite *Chrysanthemum cinerariifolium*, affect the central nervous system of warm-blooded animals, and paralyse respiration (*Fujitani*, Arch. Exp. Path. **61** (1909), 47; *Yamamoto*, C. 1920 III 517; *Tattersfield, Hobson* and *Gimingham*, J. Agric. Sci. **19**, 266, 433).

Alkaline hydrolysis of these compounds which are esters, gives pyrethrolone (I), $C_{11}H_{16}O_2$, b.p. 110–112°/0·1 mm (*semicarbazone* m.p. 200°), the common alcoholic constituent of both pyrethrins, chrysanthemum-monocarboxylic acid (II), b.p. 135°/12 mm (p. 26), and the dicarboxylic acid, m.p. 164°. which is derived from chrysanthemum-dicarboxylic acid monomethyl ester (III) (p. 33), b.p. 140°/0·5 mm. (*Staudinger* and *Ruzicka*, Helv. 7. 177):

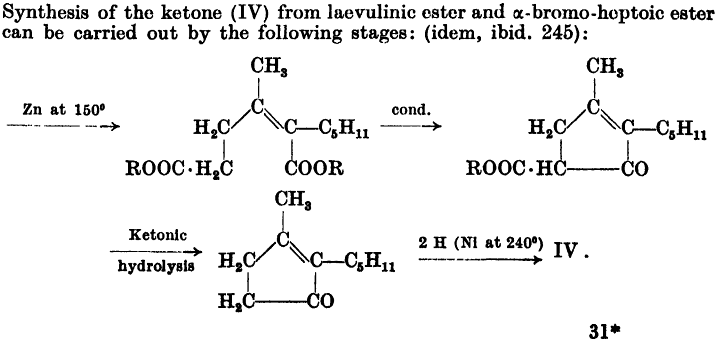




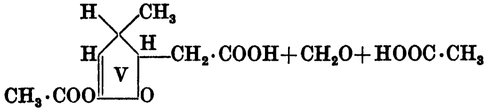
The formation of an osazone from pyrethrolone shows that the hydroxyl is adjacent to the carbonyl group. After saturation of the double bonds by the Paal-Skita method to give the tetrahydro-compound, $C_{11}H_{20}O_2$, b.p. 160–162°/10 mm., the side-chain can be oxidised away with permanganate as caproic acid, b.p. 91°/12 mm. Tetrahydro-pyrethrone (IV) (p. 56), $C_{11}H_{20}O$, b.p. 101°/12 mm. (semicarbazone m.p. 160° and 194°), obtained by reduction of the secondary alcohol group of tetrahydro-pyrethrolone, is oxidised by the same reagent to laevulinic acid, b.p. 130°/12 mm., as well as caproic acid; the Beckmann rearrangement of its oxime establishes the position of the carbonyl group in the molecule (idem, Helv. 7, 212, 236):

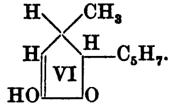


Synthesis of the ketone (IV) from laevulinic ester and α-bromo-heptoic ester can be carried out by the following stages: (idem, ibid. 245):



Ozonolysis of pyrethrolone acetate gives the acetyl derivative of methylcyclopentenolone-homocarboxylic acid (V), $C_{10}H_{12}O_5$, m.p. 138°, formaldehyde and acetic acid.





These products suggest the presence of an allene system. The conversion of pyrethrolone into dehydro-pyrethrolone (VI), $C_{11}H_{14}O_2$, b.p. 82°/0·05 mm., by autoxidation in an alkaline medium (idem, ibid. 212), is a typical reaction of 1:2-cyclopentanonols. For preliminary work on the synthesis of pyrethrolone, see idem, ibid. 377, 442; *Staudinger*, *Ruzicka* and *Reuss*, C. 1927 II 2282.

The constitutions of the two acids obtained from pyrethrins I and II were determined mainly by ozonolysis. Chrysanthemum-monocarboxylic acid (II) gave *l*-trans-caronic acid, $C_7H_{10}O_4$, m.p. 211°, and acetone, while the dicarboxylic acid (III) gave *l*-trans-caronic acid and pyrotartaric acid, m.p. 199°; *l*-trans-caronic acid was identified by conversion into terebic acid, m.p. 174°. Chrysanthemum-dicarboxylic acid can be decarboxylated to 2:2-dimethyl-3-propenyl-cyclopropane-1-carboxylic acid, b.p. 133°/12 mm., which on ozonolysis gives *l*-trans-caronic acid and acetaldehyde (*Staudinger* and *Ruzicka*, Helv. **7**, 201; cf. *Yamamoto*, Sci. Papers Inst. Phys. Chem. Res. **3** (1925), 193). A mixture of stereoisomeric forms of chrysanthemum-monocarboxylic acid has been synthesised from 1:1:4:4-tetramethyl-butadiene and diazoacetic ester (*Staudinger*, *Muntwyler*, *Ruzicka* and *Seibt*, Helv. **7**, 390).

The products obtained by partial synthesis from pyrethrolone and the chlorides of chrysanthemum-monocarboxylic acid and of chrysanthemum-dicarboxylic acid monomethyl ester were identical with the natural pyrethrins I and II (*Staudinger* and *Ruzicka*, ibid. 448).

Pharmacological studies showed that the individual components alone are physiologically inactive; the insecticidal properties of the esters seems to be determined by the simultaneous presence of the cyclopropane and cyclopentane rings (idem, ibid. 177).

Hydroaromatic Series

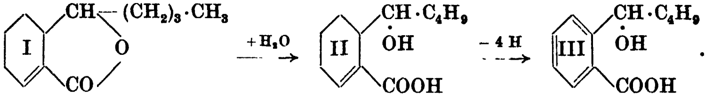
Simple members, such as **borneol** (see p. 277), **thujone** (see p. 242), etc., are known to be sudorifics (diaphoretics).

The knowledge of the action of **sabinol** (see p. 242) as an abortifacient was obtained by the Romans from the Sabines.

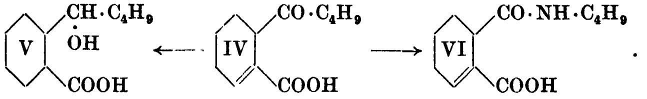
Camphor (see p. 282) causes a reversible central paralysis of the heart vagus; under certain conditions the peripheral nerves are also paralysed (*Stross*, Arch. Exp. Path. **95** (1922), 304).

Picrocrocin (bitter saffron), $C_{16}H_{26}O_7$, from *Crocus off.*, which on hydrolysis yields the terpene-aldehyde safranal, $C_{10}H_{14}O$ (constitution, see p. 354), and glucose, is one of the most widely-distributed natural abortifacients; in larger quantities it causes convulsions and also produces resorptive poisoning.

Sedanolide $C_{12}H_{18}O_2$, b.p. 147–149°/3 mm., $[\alpha]_D$—50·2°, and its isomer **cnidium-lactone**, b.p. 148–150°/2·5 mm., $[\alpha]_D$—71·88°, and **sedanonic acid**, $C_{12}H_{18}O_3$, m.p. 113° (oxime m.p. 128°), are the active constituents of celery oil and of the Chinese drug "hsiung-chuang" from *Cnidium off.*; they have narcotic properties (*Murayama* and *Itagaki*, J. Pharm. Soc. Japan **1923**, no. 493, 15; *Murayama*, ibid. **1921**, no. 477, 1). These compounds are unsaturated and hydrolysis of the lactone ring of either of the two former substances leads to the corresponding unsaturated hydroxy-acid; thus sedanolide (I) can be reduced to dihydro-sedanolide, b.p. 141–142°/3 mm., m.p. 30°, and cnidium-lactone to dihydro-cnidium-lactone b.p. 131–133°/3 mm., m.p. 51° and sedanolide can be hydrolysed to sedanolic acid (II), $C_{12}H_{20}O_3$, which can be dehydrogenated to the aromatic hydroxy-acid (III), $C_{12}H_{16}O_3$ (*Ciamician* and *Silber*, Ber. **30**, 1419, 1427; *Noguchi*, J. Pharm. Soc. Japan **54** (1934), 171):



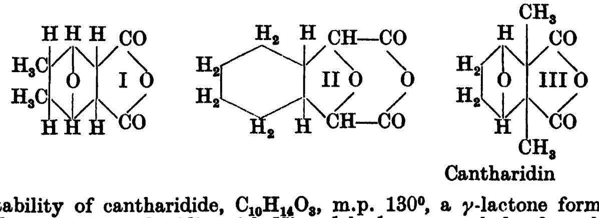
Structure (III) was confirmed by further degradation of the compound to phenyl-glyoxylic acid, phthalic acid, valeric acid, succinic acid and oxalic acid. Cnidium-lactone, sedanolide and sedanonic acid (IV) all give the same saturated hydroxy-acid (V), $C_{12}H_{22}O_3$, m.p. 131°, on reduction with Na and alcohol. The proof that sedanonic acid is the ketonic acid corresponding to sedanolic acid was given by the Beckmann rearrangement of its oxime to Δ^6-tetrahydrophthalic acid n-butylamide (VI), m.p. 171° (*Ciamician* and *Silber*, Ber. **30**, 492, 501, 1424):



The 6-ring of sedanonic acid is broken by oxidation with permanganate, and glutaric, valeric and oxalic acids are obtained.

Cantharidin, $C_{10}H_{12}O_4$, m.p. 218°, is contained in the genital glands of the so-called Spanish flies, which are beetles belonging to the genera *Lytta* and *Meloe* (*Colledge*, Pharm. J. (4) **30** (1910), 674), and also in several species from Java, *Horia Debyei*, *Cisetes maxillosa* and *Epicauta ruficeps* (*van Zijp*, Pharm. Weekblad **54** (1917), 295; **59** (1922), 285; *Stern*, C. 1932 II 557). It is used for plasters because of its blistering action (for physiological test, see van Zijp, loc. cit.), and is also a strong kidney poison, though chickens and hedgehogs seem to be little affected by it (*Ellinger*, Arch. Exp. Path. **58**, 424; *Forni*, Arch. Farm. Sperim. **18** (1914), 107). The oestrogenic action produced by subcutaneous injection (*Stern*, Arch. Exp. Path. **166** (1932), 395) is probably due to the presence of traces of sex hormones.

Cantharidin has been shown by titration to be an anhydride (*Danckwortt*, Arch. Pharm. **252** (1914), 663; imide m.p. 194°; hydrazide m.p. 118°; see *Meyer*, Mo. **18**, 393; *Gadamer*, Arch. Pharm. **260** (1922), 199; *Iyer* and *Guha*, J. Indian Inst. Sci. A, **14**, 31); its hydrolysis yields the dibasic cantharidinic acid (dimethyl ester m.p. 91°, see *Homolka*, Ber. **19**, 1082). The fourth O-atom in the molecule is in an ether group. Thermal degradation of cantharidin with P_2S_5 gives o-xylene (*Piccard*, Ber. **10**, 1504; **11**, 2122; **12**, 577; **19**, 1404); soda-lime distillation gives cantharene (dihydro-o-xylene, see p. 97; *Gadamer*, Arch. Pharm. **255** (1917), 315). These facts suggest one of the following formulae (I–III) for cantharidin:

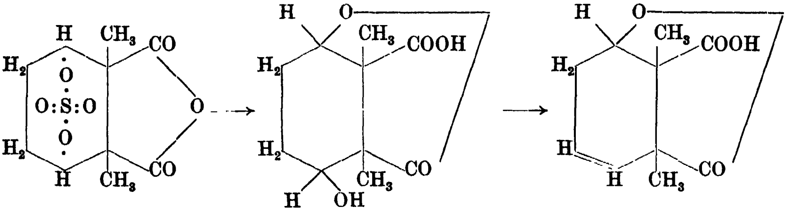


Cantharidin

The stability of cantharidide, $C_{10}H_{14}O_3$, m.p. 130°, a γ-lactone formed by the reduction of cantharidin with Ni and hydrogen, excludes formula (II).

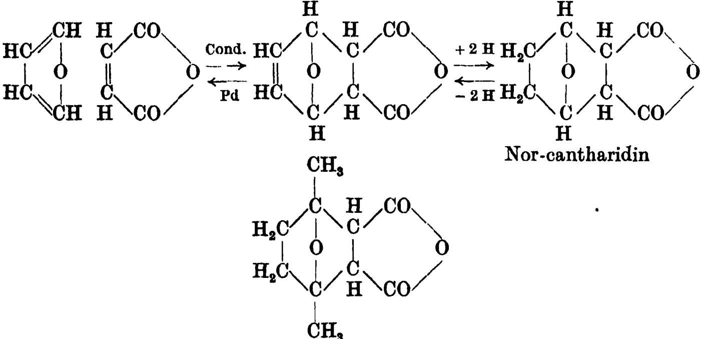
Elimination of the oxygen-bridge via the dibromide $C_{10}H_{12}O_3Br_2$ leads to deoxy-cantharidinic acid, $C_{10}H_{14}O_4$, which is easily converted into its anhydride, deoxy-cantharidin, $C_{10}H_{12}O_3$, m.p. 164° (decomp.) (*Gadamer*, Arch. Pharm. **255** (1917), 290; **252** (1914), 636). The synthetic deoxy-cantharidinic acids corresponding to (I) and (II) above are not identical with that from the natural product, and hence cantharidin must have formula (III) (*Coffey*, Rec. **42** (1933), 387, 1026).

The oxygen bridge in the cantharidin molecule is opened by bromine or by chlorsulphonic acid, in the latter case via cantharidin sulphate, and cantharolic acid (IV), $C_{10}H_{14}O_5$, m.p. 260°, to cantharic acid (V), $C_{10}H_{12}O_4$, m.p. 276° (*Meyer*, Mo. **19**, 707; *Gadamer*, Arch. Pharm. **258** (1920), 171; *Gadamer* and *Schittny*, ibid. **260** (1922), 172):

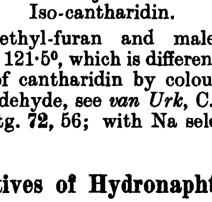


IV V

Formula (III) for cantharidin receives convincing support from the catalytic fission with Pd at 280°, which leads via dehydro-cantharidin to furan and dimethyl-maleic anhydride, m.p. 96° (*v. Bruchhausen* and *Bersch*, Arch. Pharm. **266** (1928), 697); the synthetic norcantharidin, $C_8H_8O_4$, m.p. 117°, formed from furan and maleic anhydride by the diene synthesis, followed by reduction, undergoes a similar decomposition (*Diels* and *Alder*, Ber. **62**, 554):



Nor-cantharidin



Iso-cantharidin.

Condensation of αα′-dimethyl-furan and maleic anhydride gives *iso-cantharidin*, $C_{10}H_{12}O_4$, m.p. 121·5°, which is different from the natural product.

For the identification of cantharidin by colour reactions with azo-dyes, and dimethylamino-benzaldehyde, see *van Urk*, C. 1929 II 76; with vanillin-HCl, see *David*, Pharm. Ztg. **72**, 56; with Na selenite, see *Klein*, Ind. Eng. Chem. **2** (1910), 389.

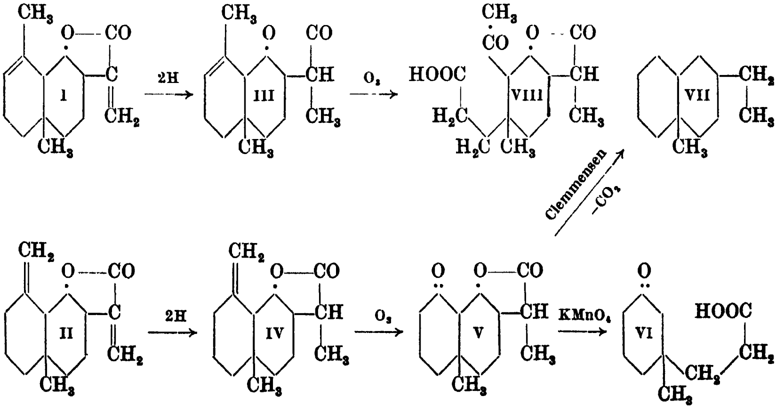
Derivatives of Hydronaphthalene

Alantolactone (I), $C_{15}H_{20}O_2$, m.p. 76°, **isoalantolactone** (II), m.p. 115°, and **dihydro-isoalantolactone**, $C_{15}H_{22}O_2$, m.p. 174°, the poisonous constituents of elecampane root from *Inula helenium*, resemble the other hydronaphthalene lactones discussed later and are convulsive poisons for warm-blooded animals; they are also fish poisons and anthelmintics.

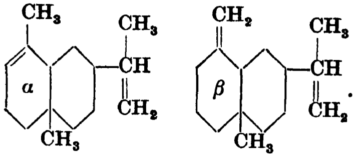
The first two compounds contain two double bonds; one of these must be in the αβ-position to the keto-group, because it is easily reduced by Na amalgam to the dihydro-compounds, $C_{15}H_{22}O_2$ (III), m.p. 126°, and (IV), m.p. 174°; this assumption receives further support from the ease of addition of ammonia and diazomethane (formation of pyrazoline derivatives) (*Hansen*, Ber. **64**, 67), and also from the velocity of esterification of the carboxylic acids obtained by the addition of HCN to these double bonds (*Hansen*, J. pr. **136**, 176). Reduction with Pt and hydrogen saturates both double bonds of alanto- and isoalantolactone, and gives from either compound the same tetrahydro-compound, $C_{15}H_{24}O_2$, m.p. 147·5°; hence they are structural isomers which differ only in the position of the second double bond.

The methyl ester (m.p. 114°) of the acid corresponding to tetrahydro-alantolactone is reduced with Na and alcohol to the corresponding glycol, b.p. 167–170°/0·4 mm.; with HI this yields a hydrocarbon, $C_{15}H_{24}$, b.p. 130–133°/12 mm., which is dehydrogenated to eudalene (1-methyl-7-isopropyl-naphthalene, picrate m.p. 101°, styphnate m.p. 118°; see *Hansen*, Ber. **64**, 943; *Ruzicka* and *van Melsen*, Helv. **14**, 397; *Ruzicka* and *Pieth*, ibid. 1990), and 1:5-dimethyl-7-isopropyl-naphthalene, b.p. 110–112°/ 0·8 mm. (picrate m.p. 116·5°, see *Ruzicka*, *Pieth*, *Reichstein* and *Ehmann*, Helv. **16**, 268). Dehydrogenation of the isomeric lactones with Se opens the lactone ring and eliminates the tertiary methyl group, to give a hydrocarbon $C_{13}H_{14}$, b.p. 134–138°/14 mm. (*Harvey*, *Heilbron* and *Wilkinson*, J. **1930**, 428), which has been identified as 1 methyl-7-ethyl-naphthalene through its picrate, m.p. 101°, its styphnate, m.p. 126°, and by its conversion into naphthalene-1:7-dicarboxylic acid, $C_{12}H_8O_4$, m.p. 296° (*Ruzicka* and *Eichenberger*, Helv. **13**, 1117; *Hansen*, Ber. **64**, 67). The increased yields of this hydrocarbon in the dehydrogenation of tetrahydro-isoalantolactone gave an indication of the presence of a semicyclic methylene group.

This assumption is confirmed by the ozonolysis of dihydro-isoalantolactone (IV), which gives formaldehyde and a keto-lactone (V), $C_{14}H_{20}O_3$, m.p. 199°. This is oxidised by $KMnO_4$ to the keto-acid (VI), $C_{10}H_{16}O_3$, m.p. 93°, and reduced by Clemmensen's method to the acid $C_{14}H_{24}O_2$, which readily loses CO_2 to give a hydrocarbon $C_{13}H_{24}$, b.p. 102°/12 mm. The hydrocarbon has been identified as 3-ethyl-9-methyl-cis-decalin (VII) (*Ruzicka*, *Koolhaas* and *Wind*, Helv. **14**, 1175), and when dehydrogenated it gives β-ethylnaphthalene (picrate m.p. 96°) (*Hansen*, Ber. **64**, 1904). The action of ozone upon dihydro-alantolactone (III) opens the ring to give the ketolactonic acid (VIII), $C_{15}H_{22}O_5$, m.p. 191° (*Ruzicka* and *Pieth*, Helv. **14**, 1092, 1456).



The alantolactones and santonin (below) are closely related in structure to the two sesquiterpenes, α- and β-selinene (p. 328):



Santonin (I, page 489), $C_{15}H_{18}O_3$, m.p. 170°, [α]D—171·4°, is the active constituent of the wormseed of *Artemisia cina* and *maritima* (*Josephson*, Svensk farm. Tid. **35** (1931), 29 *Brüning*, C. 1931 II 2477). Santonin and sodium santonate are poisons producing convulsions (*Oshika*, C. 1923 III 173); they also cause coloured vision (yellow or green: xanthopsia or chromatopsia) (*Marshall*, J. Pharm. Exp. Ther. **32** (1928), 189). For pharmacological studies on the influence of the lactone ring, the carbonyl and the double bond, see *Wedekind* (Z. med. Chem. **4** (1926), 93).

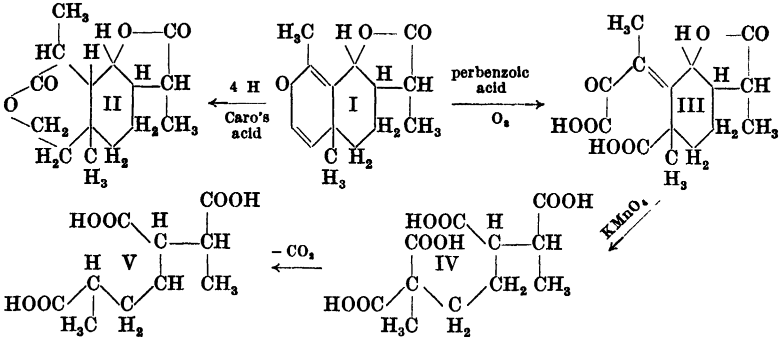
Santonin behaves like a lactone, and its third O-atom can be shown to be in a keto group (α-oxime m.p. 230°; β-oxime m.p. 217°; see *Wedekind*, Ber. **32**, 1412; *Cusmano*, Lincei (5) **21** (1912), II, 796).

Catalytic hydrogenation of santonin gives a mixture of dihydro-santonin, $C_{15}H_{20}O_3$, m.p. 105° (*Bargellini*, ibid. (5) **22** (1912), I, 443), which still contains one double bond and can be oxidised with permanganate to dihydroxy-dihydro-santonic acid, $C_{15}H_{24}O_6$ (*Wedekind*, *Goost* and *Jäckh*, Ber. **63**, 50), together with tetrahydro-santonin, $C_{15}H_{22}O_3$, m.p. 155° (*Rimini* and *Jona*, C. 1913 I 1773; *Wienhaus* and *v. Oettingen*, Ann. **397**, 219; *Asahina*, Ber. **46**, 1775), which can be reduced (Clemmensen) to desoxy-tetrahydro-santonin, $C_{15}H_{24}O_2$, m.p. 154° (*Staudinger*, *Signer* and *Schweitzer*, Ber. **64**, 398). Prolonged catalytic reduction eventually reduces the carbonyl group to the hydroxy-lactone, hexahydro-santonin, $C_{15}H_{24}O_3$, m.p. 211°. Dehydrogenation of the latter with selenium brings about loss of a tertiary methyl group and of the lactone group, and gives 1-methyl-7-ethyl-naphthalene, b.p. 95–99°/1 mm. (picrate m.p. 101°, styphnate m.p. 126°) (*Ruzicka* and *Eichenberger*, Helv. **13**, 1117; *Clemo* and *Haworth*, J. **1930**, 2579). When hexahydro-santonin is reduced with HI and P, the tertiary methyl group migrates to the position para to the other methyl group, and 1:4-dimethyl-7-ethyl-decalin, $C_{14}H_{26}$, b.p. 120–125°/20 mm., is formed (*Clemo* and *Haworth*, loc. cit.).

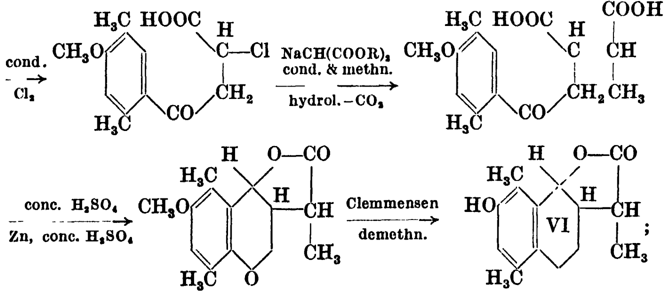
As a lactone, santonin dissolves in alkalis to give salts of santoninic acid, $C_{15}H_{20}O_4$, which on fusion with potash yields p-dimethyl-β-naphthol and propionic acid; isomerisation of santoninic acid with boiling baryta gives santonic acid, $C_{15}H_{20}O_4$, m.p. 171° (*Francesconi*, Lincei **1896**, II, 214; *Angeli* and *Marino*, ibid. **16** (1907), I, 159). Reduction of the lactone ring yields santonous acid, $C_{15}H_{20}O_3$, and 1:4-dimethyl-7-ethyl-octahydro-naphthalene, $C_{14}H_{24}$, b.p. 248°. Santonous acid has been synthesised (*Clemo*, *Haworth* and *Walton*, J. **1929**, 2368) and this synthesis fixes the position of the α-propionic side chain in santonin. For the oxidative degradation of santonic acid to aposantonic acid, $C_{14}H_{20}O_3$, m.p. 165°, see *Wedekind* and *Jackh*, J. pr. **139**, 129.

The keto-group of santonin has been shown to be in the hydronaphthalene ring by the conversion of tetrahydro-santonin by *Caro's* acid into the di-lactone tetrahydro-santonilide (II), m.p. 159·5° (*Wedekind*, Ber. **47**, 2483). The positions of the double bonds and of the lactone bridge have been established by oxidation: perbenzoic acid gives santonin-oxide, $C_{15}H_{18}O_4$, m.p. 157°, which when treated with ozone gives santonin-ketodicarboxylic acid (III), $C_{15}H_{18}O_7$, m.p. 208° the ring being opened. This is oxidised by permanganate or nitric acid to the heptane-tetracarboxylic acid (IV), $C_{11}H_{16}O_8$, m.p. 166°; its decarboxylation product, the tricarboxylic acid (V), $C_{10}H_{16}O_6$, m.p. 88°, has been synthesised from 2-methylcyclopentanone-5-carboxylic ester and α-bromopropionic ester (*Ruzicka* and *Steiner*, Helv. **17**, 614), and is degraded to succinic acid with CrO_3 (*Angeli*, Ber. **46**, 2233;

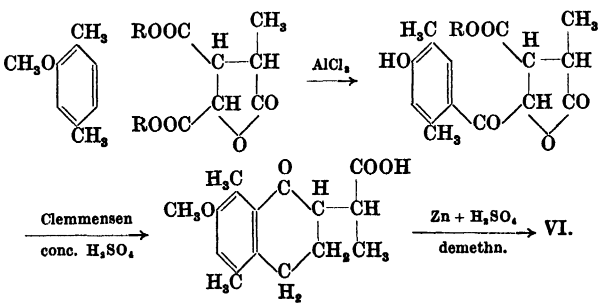
Lincei (5) 33 (1924), II, 10; *Ruzicka* and *Eichenberger*, Helv. **13**, 1120; *Wedekind* and *Tettweiler*, Ber. **64**, 1796).



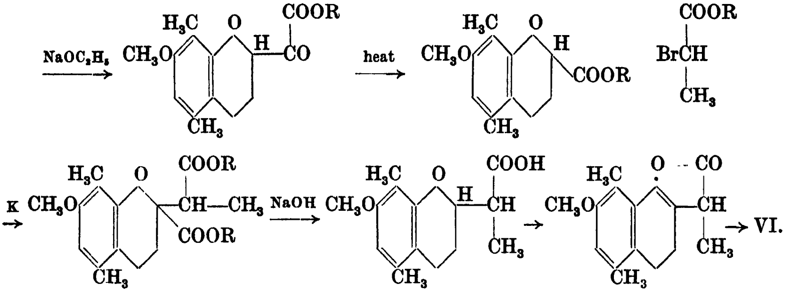
The tertiary methyl group shows a great tendency to migrate to the α-position of the hydronaphthalene ring, as in the potash fusion of santoninic acid, the HI reduction of hexahydrosantonin, and the formation of santonigenic acid. This tendency is further illustrated by the isomeric change of santonin to desmotropo-santonin (VI), m.p. 199°, in the presence of mineral acids; one ring becomes aromatic and the product is a phenol (*Andreocci* and *Bertolo*, Ber. **31**, 3131; *Wedekind* and *Schmidt*, Ber. **36**, 1386; *Francesconi*, ibid. 2667). The constitution of this phenolic lactone has been established by its syntheses: (a) from methoxy-p-xylene, succinic anhydride and sodiomalonic ester (*Clemo*, *Haworth* and *Walton*, J. **1930**, 1110):



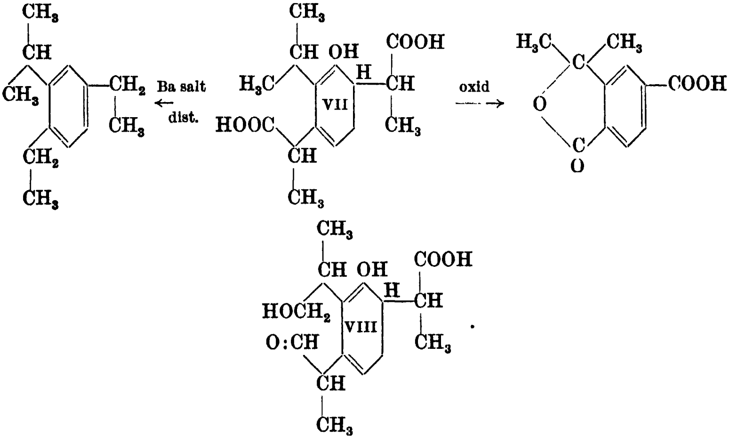
(b) from methoxy-p-xylene, methylsuccinic ester and oxalic ester (*Chitchibabin* and *Shtchukina*, Ber. **63**, 2793):



(c) from 1:4-dimethyl-2-methoxy-α-tetralone, oxalic ester and α-bromopropionic ester (Brit. Pat. 341,402):



Santonin is hydrolysed in a curious way when exposed to light in acetic acid solution and gives photo-santonic acid (VII), $C_{15}H_{22}O_5$, and isophoto-santonic acid (VIII). Distillation of the Ba salt of the former yields 1:4-diethyl-2-isopropyl-benzene, and its oxidation gives dimethyl-phthalide-carboxylic acid (*Francesconi* and *Venditti*, Gazz. **32** (1902), I, 281; *Banchi*, ibid. **58** (1928), 77; *Banchi* and *Infante*, ibid. **61** (1931), 839):



Synthetic model-compounds prepared from β-tetralone and β-bromopropionic ester by the Reformatsky reaction, or from cyclohexanone or β-tetralone and pyrotartaric ester (Germ. Pat. 622,405; *Huppmann*, C. 1931 I 2756; *Bergs*, Germ. Pat. 526,000; French Pat. 716,890) have an action similar to that of santonin (*Bergs*, Ber. **63**, 1285; French Pat. 716,890).

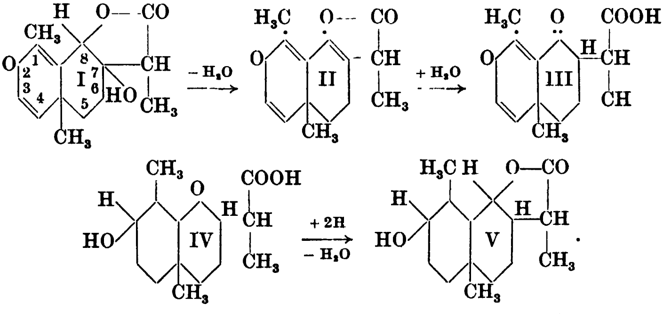
Artemisin (I, = 7-hydroxy-santonin), $C_{15}H_{18}O_4$, m.p. 203°, is obtained from the mother liquors in the preparation of santonin from *Artemisia maritima*, and shows a similar physiological action (*Freund* and *Mai*, Ber. **34**, 3717; *Bertolo*, Gazz. **34** (1904), II, 322).

Distillation of artemisin with Zn dust gives 1:4-dimethylnaphthalene (*Freund* and *Mai*, loc. cit.), while dehydrogenation of its tetrahydro-compound with Se gives 1-methyl-7-ethyl-naphthalene, b.p. 130–135°/16 mm. (picrate m.p. 97°, styphnate m.p. 126°); hence the same carbon skeleton is present as in santonin.

Artemisin (oxime of its acetyl derivative, m.p. 199°), has two double bonds, like santonin, and is reduced by Pd and hydrogen to four isomeric tetrahydro-artemisins, $C_{15}H_{22}O_4$: α, m.p. 192°, β, m.p. 169°, γ, m.p. 224° (oxime m.p. 256°), and δ, m.p. 208° (oxime m.p. 185°); the α form is reduced by amalgamated Zn and HCl (Clemmenson) to two isomeric deoxy-tetrahydro-artemisins, $C_{15}H_{24}O_3$, m.ps. 205° and 228°. Energetic reduction with platinum oxide and hydrogen reduces the carbonyl group to a secondary alcohol group, with the formation of two isomeric hexahydro-artemisins, $C_{15}H_{24}O_4$, m.ps. 208° and 242°.

With Caro's acid, tetrahydro-artemisin gives the hydroxydilactone $C_{15}H_{22}O_5$, m.p. 224°, which corresponds to tetrahydro-santonilide; this reaction requires a methylene group adjacent to the keto-group, and since artemisin itself does not give the reaction, one of the double bonds must be in the 3:4-position. Alkaline fission of artemisin leads to artemisinic acid, $C_{15}H_{20}O_5$, m.p. 135°, which differs from santoninic acid in that when fused with potash it gives 1:4-dimethyl-7-ethyl-β-naphthol, $C_{14}H_{16}O$, m.p. 126°, and CO_2 (*Bertolo*, Gazz. **56** (1926), 856). Artemisin behaves like santonin in giving an isomeric desmotropo-artemisinic acid, m.p. 236° (diacetate m.p. 150°) (*Bertolo*, Gazz. **50** (1920), I, 114).

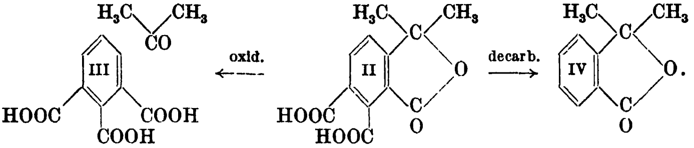
The fourth O-atom of artemisin is present in a hydroxyl group which is shown by the formation of monoacetyl-artemisin and diacetyl-desmotropo-artemisin; this group is eliminated by the action of formic acid and high vacuum distillation to give the triply unsaturated artemisene (II), $C_{15}H_{16}O_3$, m.p. 182°. The ease of dehydration indicates that the hydroxyl is tertiary (on C_7); dehydration also takes place by the action of alkali upon artemisin and its derivatives, followed by hydration in another direction to yield a second keto-group on C_8. With artemisin (I), the reaction runs via artemisene (II) to artemionic acid (III), $C_{15}H_{18}O_4$, m.p. 208°. Its hexahydro-derivative (IV), $C_{15}H_{22}O_4$, m.p. 179°, is reduced by Na amalgam to a compound (V), $C_{15}H\,_{4}O_3$, m.p. 206°, identical with hexahydro-santonin (*Tettweiler*, *Engel* and *Wedekind*, Ann. **492**, 105):



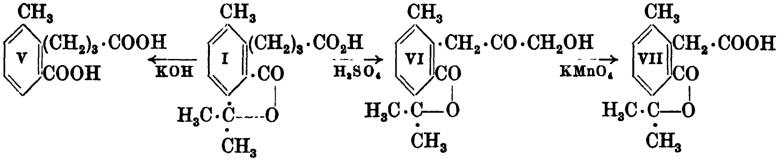
"Picrotoxin", $C_{30}H_{34}O_{13}$, m.p. 200°, is possibly a molecular compound and is the convulsive poison and fish poison (*Chistoni*, Arch. farm. sperim. **12** (1911), 385; **13** (1912), 220) of the so-called Cocculus berries, the fruits of the East Indian creeper *Menispermum cocculus* and *Anamirta panniculata*. From it two dilactones can be isolated, **picrotoxin**, $C_{15}H_{16}O_6$, m.p. 201°, and **picrotin**, $C_{15}H_{18}O_7$, m.p. 250°, the constitutions of which are not yet settled (*Meyer* and *Bruger*, Ber. **31**, 2958; *Horrmann*, Ber. **45**, 2090). When hydrolysed they give the corresponding lactonic acids and related dicarboxylic acids, α- and β-picrotoxininic acids, $C_{15}H_{18}O_7$, m.ps. 209° and 231°, and picrotoxinin-dicarboxylic acid, $C_{15}H_{20}O_8$, decomp. 163°, and α- and β-picrotinic acids, $C_{15}H_{20}O_8$, m.ps. 245° and 254°, and picrotin-dicarboxylic acid, $C_{15}H_{22}O_9$, m.p. 271°, with picrolactone, $C_{15}H_{18}O_7$, m.p. 339° (*Horrmann*, Ann. **411**, 273).

Reduction of the lactones with HI and P yields desoxo-picrotinic acid, $C_{15}H_{18}O_4$, m.p. 135°, the amide of which can be degraded (Hofmann) to an amine; exhaustive methylation of this gives a neutral substance, $C_{14}H_{16}O_2$, b.p. 172–183°/13 mm., which is ozonised to acetic acid and the aldehyde, $C_{12}H_{12}O_3$, b.p. 195°/14 mm., or the corresponding monobasic acid, $C_{12}H_{12}O_4$ (*Horrmann*, Ber. **49**, 2107).

Oxidation of picrotinic acid (formula I below) with $KMnO_4$ gives an acid $C_{13}H_{12}O_6$, m.p. 175°, which with CrO_3 yields a dibasic acid $C_{12}H_{12}O_7$, m.p. 290°, and with HNO_3 and $KMnO_4$ an acid, $C_7H_{10}O_5$, m.p. 95° (*Angelico*, Gazz. **41** (1911), II, 337). Oxidation of picrotoxin with MnO_2 and H_2SO_4 forms a lactone-dicarboxylic acid (II), $C_{12}H_{10}O_6 \cdot H_2O$, m.p. 220° or 286° (dimethyl ester m.p. 103°), together with mellophanic acid, $C_{10}H_6O_8$, m.p. 241° (tetramethyl ester m.p. 132°). The constitution of the C_{12}-acid is established (a) by further degradation to benzene-1:2:3-tricarboxylic acid (III), $C_9H_6O_6$, and acetone (*Angelico*, Gazz. **42** (1912), II, 540), (b) by complete decarboxylation with Cu and quinoline to αα-dimethylphthalide (IV), $C_{10}H_{10}O_2$, m.p. 70° (*Späth*, *Wessely* and *Nadler*, Ber. **66**, 129), and (c) by partial decarboxylation to αα-dimethyl-phthalide-4-carboxylic acid (cannabinolactonic acid, cf. p. 511) (*Mercer*, *Robertson* and *Cahn*, J. **1935**, 997):



Fusion with potash decomposes picrotinic acid into acetone and a dibasic acid, $C_{12}H_{14}O_4$, m.p. 132°, which has been shown to be (V) by ring-closure with Na to 5-methyl-1-tetralone-2-carboxylic acid (idem, ibid.), while its oxidation product, picrotin-phthaldicarboxylic acid, $C_{15}H_{16}O_6$, yields acetone and a tribasic acid, $C_{12}H_{12}O_6$, m.p. 153° (*Angelico* and *Monforte*, Gazz. **53** (1923), 800).

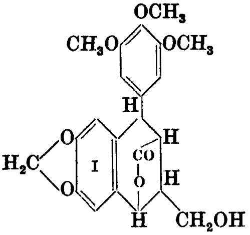


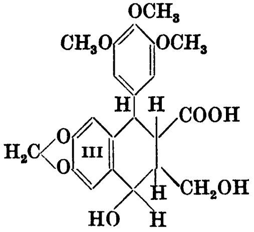
With strong sulphuric acid, α-picrotinic acid loses two C-atoms and gives picrotin-ketol (VI), $C_{14}H_{16}O_4$, m.p. 130° (acetate m.p. 84°; oxime m.p. 206°), which is oxidised by permanganate to a monobasic acid (VII), $C_{13}H_{14}O_4$, m.p. 165° (*Horrmann* and *Hagedorn*, Arch. Pharm. **259** (1921), 7; *Mercer* and *Robertson*, J. **1936**, 288).

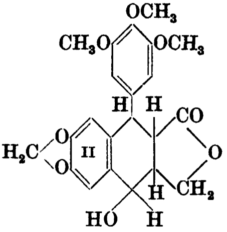
Picrotoxinin is degraded by HI or HCl to picrotin-ketone, $C_{14}H_{16}O_3$, b.p. 190°/8 mm. (*Angelico*, Gazz. **41** (1911), II, 337; *Angelico* and *Monforte*, ibid. **53** (1923), 800), or to the chloroketone, $C_{14}H_{15}O_3Cl$; action of alkali leads, via tetramethyl-phthalide, $C_{12}H_{14}O_2$, m.p. 81°, to 1:2-dimethyl-benzene-3-carboxylic acid, $C_9H_{10}O_2$, m.p. 144° (*Angelico*, Gazz. **42** (1912), II, 540), while HI gives the hydrocarbon $C_{12}H_{20}$, b.p. 95°/9 mm. (*Sielisch*, Ber. **45**, 2555). Ozonolysis yields formic acid and the dilactone of picrotoxininone-dicarboxylic acid, $C_{14}H_{18}O_9$, picrotoxininone, $C_{14}H_{14}O_7$, m.p. 145° and 242° (*Horrmann*, Arch. Pharm. **258** (1920), 200). Ozonolysis of α-picrotoxininic acid also gives formic acid and picrotoxinonic acid, $C_{14}H_{16}O_8$, decomp. 225–260° (*Horrmann* and *Wächter*, Ber. **49**, 1554).

The rhizomes of various species of ***Podophyllum*** (Berberidaceae) of North America and northern India contain two isomeric compounds, $C_{22}H_{22}O_8$, **podophyllotoxin** (I, p. 493), m.p. 117°, $[\alpha]_D - 94{\cdot}4°$ (acetate m.p. 181°), and **picropodophyllin** (II), m.p. 228°, $[\alpha]_D + 9{\cdot}5°$ (acetate m.p. 216°), which possess a strong purgative action.

The results obtained by oxidation and reduction, by pyrogenic dehydrogenation, and by acetylation lead to the following formulae for podophyllotoxin (I) and picropodophyllin (II) (*Borsche* and *Niemann*, Ann. **499**, 59; *R. D. Haworth, Richardson* and *Sheldrick*, J. **1935**, 1576):

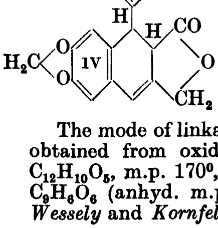


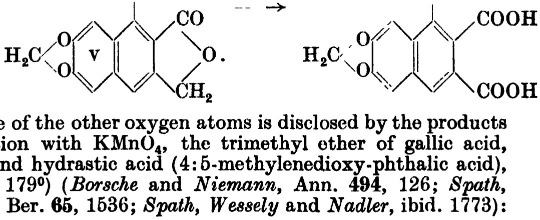




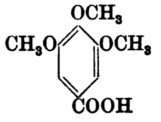
Both are hydroxy-lactones, and are derived from the same hydroxy-acid, podophyllic acid (III), $C_{22}H_{24}O_9$, m.p. 150°. Acetylation of podophyllotoxin with acetic anhydride and conc. H_2SO_4 gives a normal acetate, while with picropodophyllin dehydration takes place to the unsaturated stereoisomeric apo-picropodophyllins (IV), $C_{22}H\ _{0}O_7$, m.ps. 216° and 244° (see *Robertson* and *Waters*, J. **1933**, 83), which can be hydrolysed by alkali to the same apo-podophyllic acid, $C_{22}H_{22}O_8$, m.p. 165°.

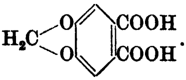
The structural formulae explain at once the formation of pyromellitic acid, $C_{10}H_6O_8$, by the oxidation of the demethylated podophyllin, the pyrogallol nucleus of which can be readily oxidised away completely; this is in contrast to the result of the HNO -oxidation of the methoxylated anhydro-dehydro-podophyllin (V), $C_{22}H_{18}O_7$, m.p. 266°, obtained by the action of Pd at 230°, which leads to benzene-pentacarboxylic acid, $C_{11}H_6O_{10}$ (pentamethyl ester m.p. 150°) (*Spath, Wessely* and *Kornfeld*, Ber. **65**, 1536). Anhydro-dehydro-podophyllin (V) has been synthesized by *Haworth* and *Richardson* (J. **1936**, 348) and this synthesis provides a rigid proof of the carbon frame-work in podophyllotoxin and picropodophyllin and of the positions of the carboxyl and primary group, and an indirect proof of the position of the secondary alcoholic group. For a synthesis of the lactone isomeric with (V), m.p. 288–289°, in which the CO and CH_2 groups are interchanged, from trimethoxy-benzoyl-succinic ester, piperonal and formaldehyde, via the corresponding dicarboxylic acid, $C_{22}H_{18}O_9$ (anhyd. m.p. 300°, dimethyl ester m.p. 207°), see *R. D. Haworth, Richardson* and *Sheldrick* (J. **1935**, 1576).

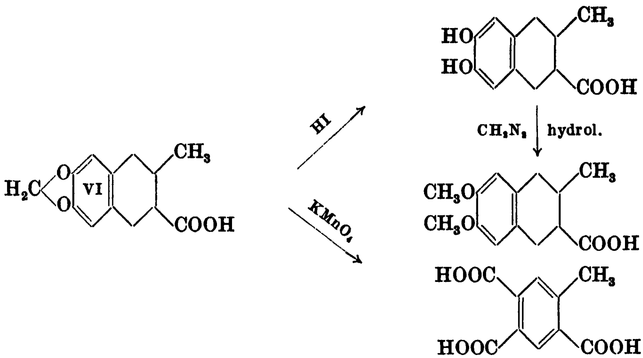




The mode of linkage of the other oxygen atoms is disclosed by the products obtained from oxidation with $KMnO_4$, the trimethyl ether of gallic acid, $C_{12}H_{10}O_5$, m.p. 170°, and hydrastic acid (4:5-methylenedioxy-phthalic acid), $C_9H_6O_6$ (anhyd. m.p. 179°) (*Borsche* and *Niemann*, Ann. **494**, 126; *Spath, Wessely* and *Kornfeld*, Ber. **65**, 1536; *Spath, Wessely* and *Nadler*, ibid. 1773):



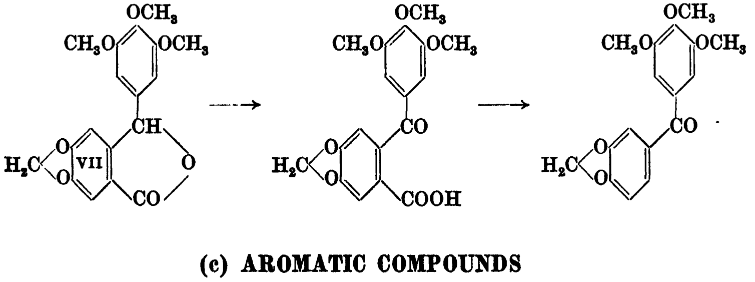




In podophyllotoxin and picropodophyllin the presence of a hydronaphthalene nucleus was proved by the formation of podophyllomeronic acid (VI), $C_{13}H_{14}O_4$, m.p. 237°, by fission with HI, that this acid is 2:3-methylenedihydroxy-7-methyl-tetralin-6-carboxylic acid is proved (a) by its degradation successively to phyllomeronic acid, $C_{12}H_{10}O_4$, m.p. 244° (dimethyl ether methyl ester m.p. 126°), phyllomerol, $C_{11}H_{10}O_2$, m.p. 162°, and β-methyl-naphthalene, $C_{11}H_{10}$, m.p. 32°; (b) by the conversion of the dimethyl ether of phyllomeronic acid, $C_{14}H_{14}O_4$, m.p. 228°, to the corresponding amine, $C_{13}H_{15}O_2N$, m.p. 205°, and then to m-hemipinic acid (4:5-dimethoxy-phthalic acid), $C_{10}H_8O_5$ (anhyd. m.p. 179°); (c) from its oxidation with $KMnO_4$ to toluene-2:4:5-tricarboxylic acid, $C_{10}H_8O_6$, m.p. 200°, and pyromellitic acid, $C_{10}H_6O_8$, m.p. 230–240° (tetramethyl ester m.p. 143°) (*Borsche* and *Niemann*, Ber. **65**, 1633) (see formulae above).

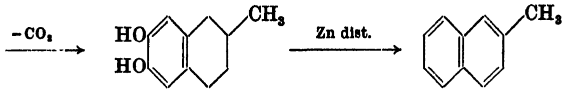
Podophyllomerol, $C_{12}H_{10}O_2$, m.p. 129°, the decarboxylation product of the acid (VI), has been synthesised from veratrol and methylsuccinic anhydride (*Robertson* and *Waters*, J. **1933**, 83; *Borsche* and *Niemann*, Ann. **502**, 264).

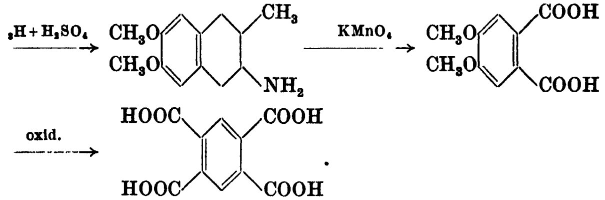
The position of the trimethoxy-phenyl residue in the 1- or 4-position of the hydrogenated ring of the tetralin nucleus is shown by the oxidation of both substances with $KMnO_4$ to ω-(3′:4′:5′-trimethoxyphenyl)-4:5-methylenedioxy-phthalide (VII), $C_{18}H_{16}O_7$ (*Borsche* and *Niemann*, Ann. **499**, 59) or to the corresponding ketonic acid, $C_{18}H_{16}O_8$, m.p. 216° (methyl ester m.p. 103°); the constitution of this acid has been established by decarboxylation to 3:4:5-trimethoxy-3′:4′-methylenedioxy-benzophenone, $C_{17}H_{16}O_6$, m.p. 127° (*Spath*, *Wessely* and *Nadler*, Ber. **66**, 125):



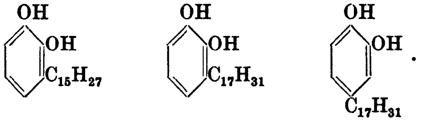
(c) AROMATIC COMPOUNDS

Some of these compounds have been described in the sections dealing with the glycosides, the tannins and the natural colouring matters.

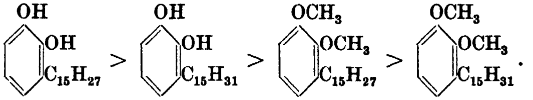




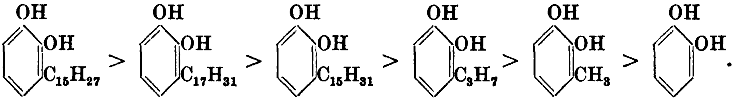
The resinous secretions of the so-called lac tree of the East (China, Indochina, Siam, Burma), are used in the manufacture of varnishes; they often cause severe inflammations of the skin, but different people show very different sensitivity to their action (*Majima*, Ber. 58, 208). The chief constituents of this resin are **urushiol, laccol** and **thitsiol** (see p. 394):



Pharmacological tests upon urushiol have shown that the physiological effect is decreased by methylation of the phenolic hydroxyl group and by saturation of the olefinic side-chain. The activities are in the following order:

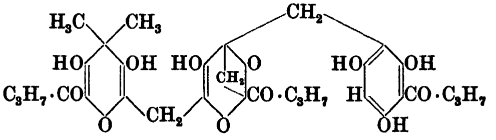


The influence of the length of the alkyl side-chain is shown by the following series:

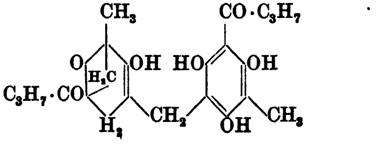


Several substances prepared from the fern *Aspidium filix mas*, such as **filicic acid** (I) and **flavaspidic acid** (II) (see p. 399):

(I)

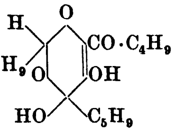


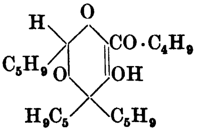
(II)



have haemolytic properties (*Pennetti*, C. 1927 I 1855; *Jodlbauer*, Arch. Exp. Path. **164** (1931), 457); they are also poisonous to fish (*Wasicky*, ibid. **97**, (1923), 454), and have an anthelmintic action (*Rath*, ibid. **141** (1929), 129).

The bitter substances from the hop, *Humulus lupulus*, viz. **humulone** and **lupulone** (see pp. 400, 401),

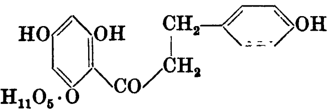


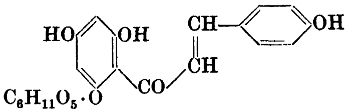


are weak hypnotics and sedatives.

Rottlerin, a yellow colouring matter which is used in India under the name of "kamala" and is obtained from the seed capsules of *Mallotus philippensis*, causes paralysis of the motor nerves and respiratory centres (*Dutt*, J. **127**, 2044); it has a fatal effect upon the frog's heart (*Dutt* and *Goswami*, J. Indian Chem. Soc. **5** (1928), 21), and has also proved to be a poison for earthworms (*Nagamachi*, C. 1923 III 270). The compound is a phenol; for degradations which show the presence in the molecule of a dimethyl-chromen nucleus, see *McGookin*, *Reed* and *Robertson*, J. **1937**, 748.

The glucosides **phlorrhizin** (p. 359), from the bark, and particularly from the roots, of various fruit-trees (*Rosaceae*), and **salipurposide** (dehydrophlorrhizin, p. 436), from species of *Salix*

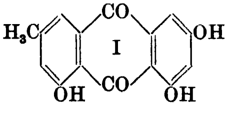


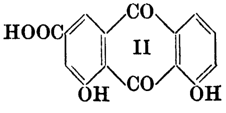


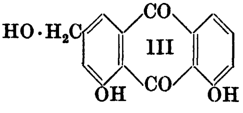
cause strong glucosuria *Charaux* and *Rabate*, Bull. Soc. Chim. Biol. **13** (1931), 814); the phenomenon can be used for a diagnostic test of the action of the kidney.

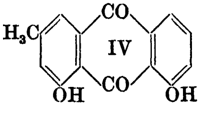
Several pungent substances of the quinone group cause a more or less marked irritation of the mucous membranes. **Plumbagin** (p. 426), a hydroxymethylnaphthaquinone from the root bark of the Indian shrub *Plumbago rosea*, is fatal to rats, guinea-pigs and frogs because of its action upon the respiratory system.

The following compounds, which are quinonoid natural colouring matters, are violent purgatives: **perezone** (p. 422), **embelin** (p. 422), the naphthaquinone **juglone** (p. 426), the glucosides of hydroxy-anthraquinones, such as **emodin** (I) from alder bark (p. 429), **rhein** (II) from rhubarb (p. 429) and **aloe-emodin** (III) from senna leaves (p. 429):









(*Casparis* and *Maeder*, C. 1925 II 1071; *Kaufmann*, Z. angew. Chem. **40**, 831); **chrysophanic acid** (IV) from *Andira araroba* has also an effect on the kidneys.

The corresponding anthranol-glucosides (see p. 363) are also purgatives (*Rosenthaler*, Apoth.-Ztg. **47** (1932), 1167).

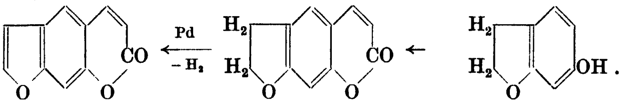
d) COUMARIN AND BENZOPYRAN DERIVATIVES[1]

Derivatives of Coumarin

The nitrogen-free fish-poisons and insecticides which are classified in this group are peculiar to the families *Rutaceae* and *Umbelliferae*, and are derived from coumarin. In most of them the coumarin skeleton is condensed with a furan ring.

6:7-*Furocoumarin* (psoralene) contains the basic structure of the following natural products: bergaptol (bergapten), xanthotoxin, isopimpinellin, peucedanin (oreoselone), imperatorin (iso-imperatorin), oxypeucedanin and ostruthol.

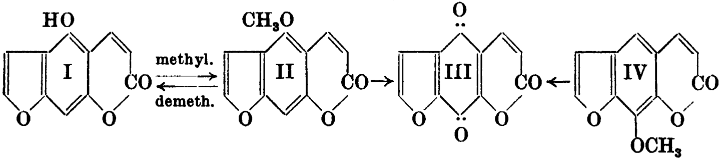
Psoralene, $C_{11}H_6O_3$, m.p. 170°, an isomer of angelicin (see below), was first isolated from the seeds of the Indian plant *Psoralea corylifolia*, which also contain angelicin (*Jois*, *Manjunath* and *Rao*, J. Indian Chem. Soc. **10** (1933), 41). It is identical with **ficusin** from the leaves of *Ficus carica* (*Späth*, *Okahara* and *Kuffner*, Ber. **70**, 73; *Jois* and *Manjunath*, ibid. 434). That it is 6:7-furocoumarin was proved by *Spath* and his co-workers by condensing malic acid with 6-hydroxy-2:3-dihydrocoumarone and dehydrogenating the resulting dihydro-psoralene, m. p. 204°, with Pd (Ber. **69**, 1087).



Psoralene Dihydro-psoralene

The active constituents of the oil of bergamot from *Citrus bergamia*, the root of which is used by the natives of the Togos as an abortifacient and as a fish-poison, are **bergaptol** (I), $C_{11}H_6O_4$, m.p. 282° (*Spath* and *Socias*, Ber. **67**, 59), and its methyl ether, **bergapten** (heraclin) (II), $C_{12}H_8O_4$, m.p. 191°. The latter has also been isolated from *Heracleum sphondylium* (*Spath* and *Raschka*, Ber. **67**, 62).

Fusion of bergapten with potash yields phloroglucinol, $C_6H_6O_3$, m.p. 208°; one of the phenolic hydroxyls is methylated, a second is present in a lactone group, as is shown by hydrolysis to bergaptenic acid, $C_{12}H_{10}O_5$ (methyl ether methyl ester m.p. 52°), while the third is in an ether group (*Pomeranz*, Mo. **12**, 379). The formation of a tribromo-compound, $C_{12}H_7O_4Br_3$ (idem, ibid. **14**, 28), which is formed by substitution of one Br, and addition of two Br to a double bond, shows that the compound contains a condensed coumarin-furan system (I). Introduction of a nitro-group in the *p*-position to the methoxyl, giving nitro-bergapten, m.p. 230–260°, reduction to amino-bergapten, m.p. 198°, followed by oxidation with bichromate and sulphuric acid to the yellow quinone (III), $C_{11}H_4O_5$, m.p. 250° (hydroquinone, $C_{11}H_6O_5$, diacetate m.p. 209°), confirms the above deduction (*Thoms*, Ber. **44**, 3327; *Thoms* and *Baetcke*, Ber. **45**, 3705):



The structures of bergaptol and bergapten have been completely established by the synthesis of the former from 3:4:6-triacetoxy-coumaran and Na-formylacetic ester (*Spath* and *Kubiczek*, Ber. **70**, 1253) and of the latter from apoxanthoxyletin (*Howell* and *Robertson*, J. **1937**, 293) and also by the methylation of synthetic bergaptol (*Späth*, *Wessely* and *Kubiczek*, Ber. **70**, 478).

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[1] For a summary of recent work see *Späth*. Ber. **70 A**, 83.

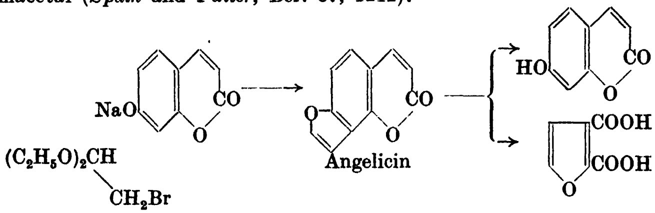
The pods of *Fagara xanthoxyloides* contain, in addition to bergapten (II) the isomeric **xanthotoxin** (IV), $C_{12}H_8O_4$, m.p. 146°. That this compound has the constitution (IV) is shown (a) by the presence of 1:2:3-pyrogallol-4-carboxylic acid in the products of its alkali fusion; (b) by its conversion into nitroxanthotoxin, m.p. 233°, amino-xanthotoxin, m.p. 236°, and finally into the same quinone (III), m.p. 250°, as that obtained from bergapten (IV) (*Thoms*, Ber. **44**, 3325; *Thoms* and *Baetcke*, Ber. **45**, 3705); (c) by its synthesis from 6:7-dihydroxy-coumaranone-3 (*Spath* and *Pailer*, Ber. **69**, 677).

Xanthotoxin is an active fish-poison, and like bergapten affects the central nervous system (*Thoms*, Ber. **44**, 3331).

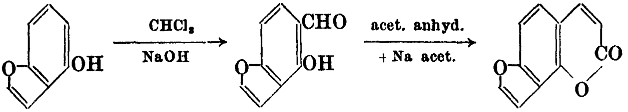
Xanthotoxol, m. p. 251—252°, the phenol related to xanthotoxin, occurs in the seeds of *Angelica Archangelica* and has been synthesized (*Späth* and *Vierhapper*, Ber. **70.** 248).

Angelicin, *isopsoralene*, $C_{11}H_6O_3$, m.p. 142°, isolated from angelica root (*Angelica Archangelica*) and from the wax of *Psoralea corylifolia*, is also a coumarin derivative. It is 7:8-furocoumarin, as shown by its oxidation with alkaline H_2O_2 to furan-2:3-dicarboxylic acid, $C_6H_4O_5$, and with $KMnO_4$ to 7-hydroxy-coumarin (umbelliferone) (*Spath* and *Pesta*, Ber. **67**, 853).

Angelicin has been synthesised from the Na salt of umbelliferone and bromacetal (*Spath* and *Pailer*, Ber. **67**, 1212):

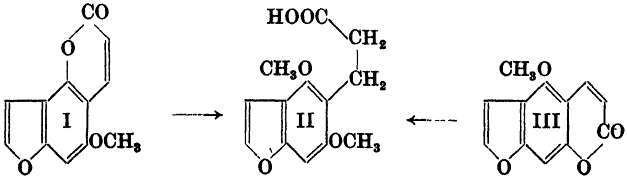


and from the Na salt of umbelliferone-aldehyde and iodoacetic acid (idem, Ber. **68**, 940). A synthesis different in principle, from 4-hydroxy-coumarone, is shown in the following scheme (*Limaye*, C. 1936 II 83):



Isobergapten (I), $C_{12}H_8O_4$, m.p. 222°, pimpinellin and isopimpinellin, all of which are found it in *Pimpinella saxifraga*, are fish-poisons and derivatives of angelicin.

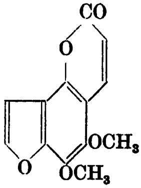
Oxidation of isobergapten with alkaline H_2O_2 gives furan-2:3-dicarboxylic acid. Reduction with Na amalgam opens the coumarin ring and reduces the double bond $\alpha\beta$-to the carboxyl group, giving dihydro-isobergaptenic acid, $C_{12}H_{12}O_5$, m.p. 147°, which is converted by rapid distillation into dihydro-isobergapten, $C_{12}H_{10}O_4$, m.p. 146°. Since the monomethyl ether of dihydro-isobergaptenic acid (II) is identical with compound prepared in a similar way from bergapten (III), isobergapten can only have formula (I) (*Wessely* and *Nadler*, Mo. **60**, 141). This is confirmed by the conversion of bergaptol into isobergapten by opening the lactone ring, methylating and then closing the lactone ring (*Spath* and *Kubiczek*, Ber. **70**, 1253).



Pimpinellin, $C_{13}H_{10}O_5$, m.p. 119°, is oxidised, like isobergapten, to furan-2:3-dicarboxylic acid. Similarly it yields a dihydro-compound, m.p. 88°, on reduction with Na amalgam. The action of dimethyl sulphate and alkali gives the methyl ester of the corresponding coumarinic acid.

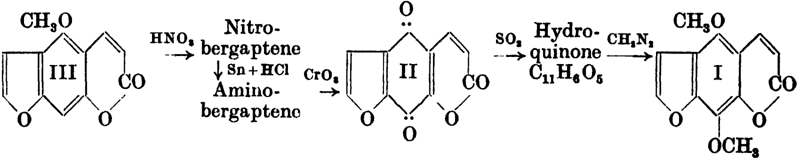
$$C_{10}H_4\left\{\begin{array}{l}OH\\COOH\\(OCH_3)_2\end{array}\right.$$

From its reactions, pimpinellin is formulated as a methoxyisobergapten (*Wessely* and *Kallab,* Mo. **59**, 161):

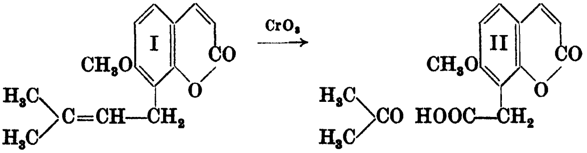


For the constitutions of the two dimeric irradiation products of pimpinellin, m.ps. 238° and 257°, see *Wessely* and *Dinjaski,* Mo. **64**, 131.

Isopimpinellin (I), $C_{13}H_{10}O_5$, m.p. 151°, which also accompanies isobergapten, has been synthesised from bergapten (III) via the quinone (II), as shown below, and hence has the constitution (I) (*Wessely* and *Kallab,* Mo. **59**, 161):



Osthol (I), $C_{15}H_{16}O_3$, m.p. 85°, is found together with oxypeucedanin and ostruthin in the poisonous Umbelliferae *Imperatoria ostruthium* and *Archangelica off.* (*Böcker* and *Hahn,* J. pr. **83**, 243). It contains a double bond which can be reduced catalytically with Pd to dihydro-osthol m.p. 85°, and a double bond $\alpha\beta$- to a carboxyl group, which is reduced by Na amalgam to the dihydro-acid $C_{15}H_{20}O_4$, m.p. 88°. The position of the methoxyl group was shown by the oxidation of osthol to 2-hydroxy-4-methoxy-benzoic acid, $C_8H_8O_4$, m.p. 155°, and the length of the side-chain by the degradation of the tetrahydro-compound, $C_{15}H_{20}O_3$, b.p. 145–150°/0·006 mm., to isocaproic acid. Detailed investigation of ostholic acid (II), $C_{12}H_{10}O_5$, m.p. 255° (*Butenandt* and *Marten,* Ann. **495**, 189), which is formed together with acetone in the CrO_3 oxidation of osthol, finally established the carbon skeleton. The acid can be degraded via 7-methoxy-8-methyl-coumarin, $C_{11}H_{10}O_3$, m.p. 137°, and 2-hydroxy-4-methoxy-3-methylbenzoic acid, $C_9H_{10}O_4$, m.p. 215°, to 2:6-dihydroxy-toluene, $C_7H_8O_2$, m.p. 121°, and hence the contsitutions of ostholic acid and osthol must be those shown in formulae II and I (*Späth* and *Pesta,* Ber. **66**, 754).



The constitution of dihydro-osthol as 8-isoamyl-7-methoxycoumarin is confirmed by its synthesis from the 4-monomethyl ether of tetrahydrotubanol (p. 504) by Pechmann's method (*Späth, Takei* and *Miyajima*, Ber. **67**, 262) and from tetrahydro-tubaic acid (*Haller* and *Acree*, Am. **56**, 1389). The synthesis of osthol itself has been achieved by the condensation of resorcylaldehyde 4-methyl ether with $\gamma\gamma$-dimethyl-allyl bromide, followed by coumarin ring-closure by Perkin's method (*Späth* and *Holzen*, ibid. 264).

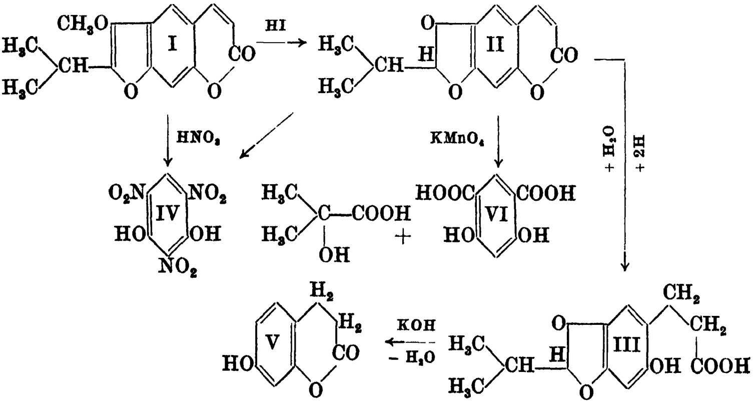
Osthenol, m. p. 124—125°, the phenol from which osthol is derived, also occurs in angelica root and on methylation gives osthol (*Späth* and *Bruck*, Ber. **70**, 1023).

The umbellifera *Peucedanum off.* contains **peucedanin**, (I), $C_{15}H_{14}O_4$, m.p. 109°, which inhibits fermentation and is a fish-poison, and its demethylated derivative, **oreoselone** (II), $C_{14}H_{12}O_4$, m.p. 174°.

Peucedanin can be converted into oreoselone with HI. In a high vacuum tetrahydro-peucedanin loses the same methoxyl group as methyl alcohol and gives a furan derivative, desoxy-oreoselone, $C_{14}H_{14}O_3$, m.p. 126°. On reduction the 5-membered oxygen ring of the latter compound opens to give a phenol, the oxidation of which yields the side-chain of the molecule as isocaproic acid (phenylhydrazide m.p. 138°) (*Spàth* and *Klager*, Ber. **66**, 749).

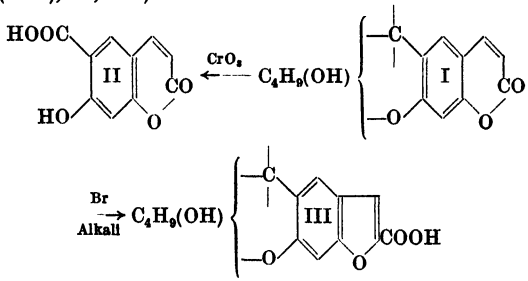
Catalytic hydrogenation of oreoselone with Pd charcoal in alkali gives dihydro-oreoselonic acid (III), $C_{14}H_{16}O_5$, m.p. 174°, which closes the lactone ring again on vacuum distillation to dihydro-oreoselone, $C_{14}H_{14}O_4$, m.p. 171°. The reduced acid is oxidised by $KMnO_4$ to succinic acid, m.p. 185°. Oreoselone does not give succinic acid on oxidation with HNO_3, but styphnic acid (IV), $C_6H_3O_8N_3$, m.p. 170°, and peucedanin behaves similarly. The presence of a coumarin ring system, which is indicated by the two last reactions, is confirmed by the potash fusion of dihydro-oreoselone, which gives 7-hydroxy-dihydro-coumarin (V), $C_9H_8O_3$, m.p. 134° (idem, ibid.).

Oxidation of oreoselone with $KMnO_4$ to α-hydroxyisobutyric acid, $C_4H_8O_3$, m.p. 71°, and α-resodicarboxylic acid (4:6-dihydroxy-isophthalic acid, VI), $C_8H_6O_6$, m.p. 306°, discloses the position of the side-chain on the coumarin nucleus, and also the part it plays in the formation of a furan ring attached to the coumarin nucleus, as is shown in formulae (I) and (II) (*Spath, Klager* and *Schlösser*, Ber. **64**, 2203):

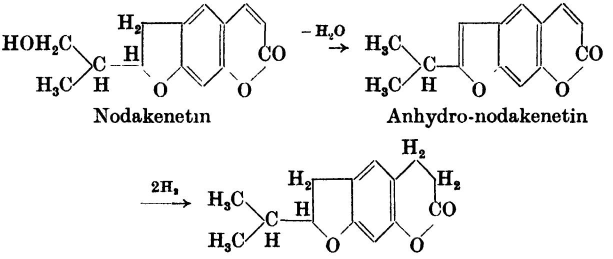


The glucoside **nodakenin**, $C_{20}H_{24}O_9 \cdot H_2O$, m.p. 216°, $[\alpha]_D + 56{\cdot}6°$ (water), from *Peucedanum decursivum*, which is used medicinally in China and Japan, can be hydrolysed into nodakenetin (I), $C_{14}H_{14}O_4$, m.p. 185°, $[\alpha]_D - 22{\cdot}4°$ (monoacetate m.p. 130°), and glucose.

Oxidation of the aglycone with CrO_3 to umbelliferone-carboxylic acid (II), $C_{10}H_6O_5$, m.p. 246°, the constitution of which is proved by degradation to umbelliferone, m.p. 231°, and by synthesis, and the rearrangement of its monobromo-substitution product into nodakilic acid (III), $C_{14}H_{14}O_5$, m.p. 215°, show the presence of a coumarin nucleus (*Arima,* Bull. Chem. Soc. Japan 4 (1929), 16, 113):



When nodakenetin is heated with P_2O_5, one mol. of water is lost and the product is anhydro-nodakenetin, $C_{14}H_{12}O_3$, m.p. 139°, which is optically inactive. This takes up 2 H_2 on catalytic hydrogenation, to give tetrahydro-anhydro-nodakenetin, m.p. 117°, which is identical with desoxo-dihydro-oreoselone. The hydroxyl group lost in the dehydration can only be attached to a methyl group of the isopropyl group; this hydroxyl is also the position of attachment of the glucose residue in the original glucoside (*Späth* and *Kainrath,* Ber. **69**, 2062):



Nodakenetin

Anhydro-nodakenetin

Desoxo-dihydro-oreoselone

Imperatorin (I), $C_{16}H_{14}O_4$, m.p. 102°, and **isoimperatorin** [I][1], m.p. 109_0, which accompany osthol in the root of *Imperatoria ostruthium,* contain a lactone group which is considered to be part of a coumarin skeleton, because it is oxidised by HNO_3 to oxalic acid, and its hexahydro-compound is oxidised to succinic acid. Oxidation with H_2O_2 gives furan-2:3-dicarboxylic acid, $C_6H_4O_5$, m.p. 223°, which shows the presence of combined coumarin and furan rings.

Fission of imperatorin and its isomer with acetic and sulphuric acids sets free the fourth O-atom, which is not ketonic, but forms an ether link between the phenolic component and an unsaturated alcohol, $C_5H_{10}O$; this is common to both compounds and can be reduced to isoamyl alcohol (trinitrobenzoate m.p. 126°). The structure of this alcohol, and the position of the double bond in it, is further established by the formation of acetone (as dibenzalacetone m.p. 113°) by the action of CrO_3 upon the original substance.

The phenol (II), $C_{11}H_6O$, m.p. 244°, obtained in this manner from imperatorin, is oxidised to pyrogallol-carboxylic acid (2:3:4-trihydroxy-benzoic acid), $C_7H_6O_5$, and gallocarboxylic acid (4:5:6-trihydroxy-benzene-1:3-dicarboxylic acid), and is identified by its methylation to xanthotoxin, $C_{12}H_8O_4$ (p. 498) (*Späth* and *Holzen*, Ber. **66**, 1137). The position of the phenol ether oxygen atom of the phenolic component of isoimperatorin [II=bergaptol], m.p. 277°, the methylation of which gives bergapten, $C_{12}H_8O_4$ (p. 497), has also been proved by the conversion of isoimperatorin into oxy-peucedanin (III) by means of perbenzoic acid (*Späth* and *Kahovec*, ibid. 1146).

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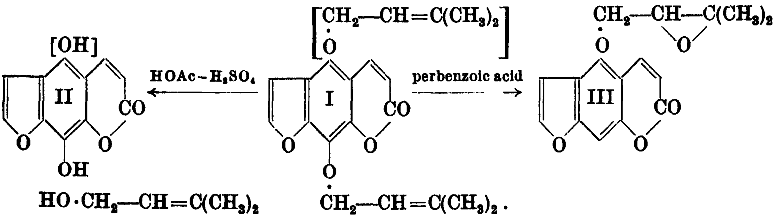
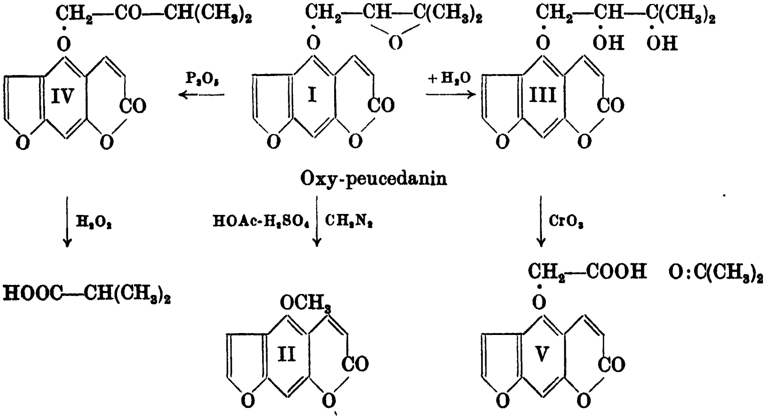
[1] This implies the formula below with the addition of the substituent in square brackets.

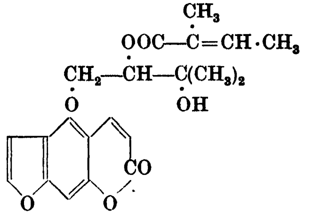


For the partial synthesis of imperatorin from the Na salt of xanthotoxol (cf. p. 498) and γγ-dimethyl-allyl bromide, see *Späth* and *Holzen*, Ber. **68**, 1123.

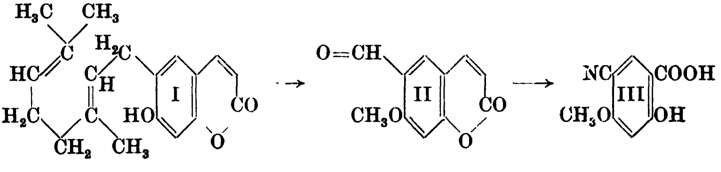
Oxypeucedanin (I), $C_{16}H_{14}O_5$, m.p. 142°, the chief poisonous constituent of *Imperatoria ostruthium*, is a closely related natural coumarin. There are three oxygen atoms present in ether groups, two of which are on the aromatic nucleus of the molecule, as is shown by the oxidation with H_2O_2 to furan-2:3-dicarboxylic acid, and by the isolation of phloroglucinol after potash fusion. The acetic-sulphuric acid fission of the substance, and the methylation of the resulting bergaptol, $C_{11}H_6O_4$, to bergapten (II; cf. also p. 497), proves the linear structure of the ring-system. The residue C_5H_9O which is split off contains the third oxygen atom in an ethylene oxide link, as is shown by the conversion of oxypeucedanin into the corresponding glycol, oxypeucedanin-hydrate, (III), $C_{16}H_{16}O_6$, m.p. 184° (diacetate m.p. 136°), and by its rearrangement into the ketone iso-oxypeucedanin (IV), m.p. 148° (oxime m.p. 186°). The fact that the side-chain is branched follows from the CrO_3-oxidation of oxypeucedanin hydrate to oxypeucedanic acid (V), $C_{13}H_8O_6$, m.p. 265° (methyl ester m.p. 185°), and acetone, and by the degradation of iso-oxypeucedanin with H_2O_2 to isobutyric acid (*Butenandt* and *Marten*, Ann. **495**, 195; *Spath* and *Klager*, Ber. **66**, 914):



Ostruthol, $C_{21}H\ _{2}O_7$, m.p. 137° (acetate m.p. 125°), a further constituent of the extract of *Imperatoria*, is hydrolysed by methyl alcoholic potash to angelic acid, $C_5H_8O_2$, m.p. 43°, and a neutral compound, $C_{16}H_{16}O_6$, m.p. 131°, which shows the properties of a coumarone-coumarin derivative; this has been shown to be identical with oxypeucedanin hydrate (see above). Since the original ester group is hydrolysed with comparative ease, ostruthol probably has the following constitution (*Späth* and *v. Christiani*, Ber. **66**, 1150):



Ostruthin (I), $C_{19}H_{22}O_3$, m.p. 119°, another constituent of *Imperatoria ostruthium*, resembles osthol in containing an olefinic side-chain attached to a coumarin ring. The action of CrO_3 upon its methyl ether, $C_{20}H_{24}O_3$, m.p. 55°, removes part of the side-chain as 2-methyl-Δ^2-hepten-6-one, $C_8H_{14}O$, b.p. 170–173°, and leaves 7-methoxy-coumarin-6-aldehyde (II), $C_{11}H_8O_4$, m.p. 256° (oxime m.p. 228°); the constitution of the latter compound is established by its degradation via 6-cyano-7-methoxy-coumarin, m.p. 282°, to 2-hydroxy-4-methoxy-5-cyano-benzoic acid (III). The position of the substituents on the aromatic nucleus of the molecule is also shown by energetic methylation with dimethyl sulphate followed by oxidation to 4:6-dimethoxy-benzene-1:3-dicarboxylic acid. Oxidation of hexahydro-ostruthin with alkaline H_2O_2 destroys the coumarin ring and gives an undecanoic acid (4:8-dimethyl-nonanoic acid), $C_{11}H_{22}O_2$; this fact throws light on the structure of the whole side-chain (*Butenandt* and *Marten*, Ann. **495**, 189; *Späth* and *Klager*, Ber. **67**, 859). The reactions can be explained by means of the following formulae:



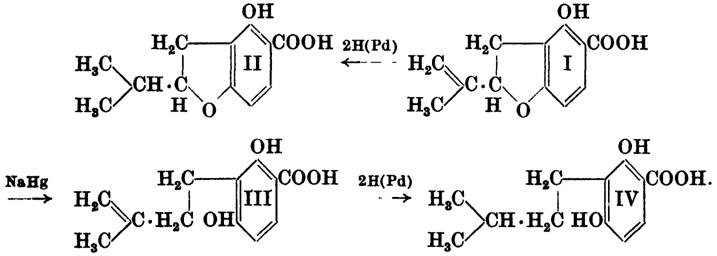
Derivatives of Benzo-pyran

The active constituents of the poisons obtained from various tropical members of the family *Papilionaceae*, such as rotenone, deguelin, tephrosin and toxicarol, differ from the fish and insect poisons discussed so far in containing a considerably more complicated ring-system.

Rotenone, which is used in the East for fishing and as an arrow-poison (*Gersdorff*, Am. **58**, 1897), is obtained from *Derris elliptica*, a tropical Papilionacea, and *Millettia tawaniana*; it is identical with the Peruvian fish-poison "cube" from *Lonchocarpus nicon* (*Clark*, Science **70** (1929), 478), and the Brazilian timbo root (*Jones*, J. Washington Acad. Sci. **23** (1933) 36), and is one of the most active vegetable fish and insect poisons known (*Kenkyujo*, Brit. Pat. 239,483; *Tattersfield* and *Gimingham*, Chem. and Ind. **46**, 368; *Gersdorff*, Am. **52**, 3440; *Takei*, *Miyajima* and *Ono*, Ber. **66**, 1826). It is accompanied in derris and cube root by the compounds deguelin, tephrosin and toxicarol, which are very similar in structure and have the same physiological action (*Kariyone* and *Atsumi*, J. Pharm. Soc. Japan **1928**, no. 491, 6; *Takei*, Biochem. Z. **157**, 1; *Butenandt*, Ann. **464**, 253; *La Forge* and *Smith*, Am. **51**, 2574). For their isolation and identification, see *Boam* and *Cahn*, J. Soc. Chem. Ind. **54** (1935), 42 T; **56** (1937), 91 T.

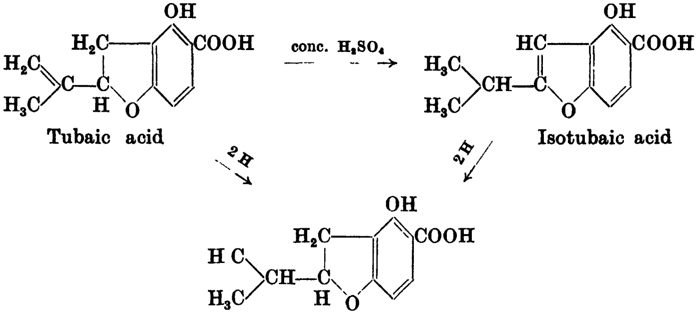
Rotenone, $C_{23}H_{22}O_6$, dimorphous, I. m.p. 163°; II. m.p. 180°, contains two methoxyl groups and a keto-group which can enolise, since it forms an enol-acetate, m.p. 135° (*Smith* and *La Forge*, Am. **54**, 2996; *Butenandt* and *Hilgetag*, Ann. **506**, 158); the remaining three O-atoms are inactive and must be present in ether links. With Pd and hydrogen one reactive double bond is reduced, giving dihydro-rotenone, $C_{23}H_{24}O_6$, which exists in two forms, m.p. 164° (labile) and m.p. 215° (stable) (*Takei*, *Koide* and *Miyajima*, Ber. **68**, 508). Energetic hydrogenation also reduces the keto-group to a methylene group to give dihydro-desoxy-rotenone, $C_{23}H_{26}O_5$, m.p. 168° (*Butenandt*, Ann. **464**, 256). Reduction of rotenone with Na amalgam destroys one centre of asymmetry (*Haller* and *La Forge*, Ann. **53**, 3426) and at the same time opens an oxygen ring; for the product, rotenonic acid, $C_{23}H_{24}O_6$, m.p. 209°, has a phenolic hydroxyl (*Butenandt*, Ann. **464**, 266; *La Forge* and *Smith*, Am. **51**, 2574) and still contains the double bond of rotenone, which can be reduced catalytically (dihydro-rotenonic acid, $C_{23}H_{26}O_6$, m.p. 206°).

The action of alcoholic potash upon rotenone gives an aromatic fission product, tubaic acid (I), $C_{12}H_{12}O_4$, m.p. 128° (*Takei* and *Koide*, Ber. **62**, 3030). Catalytic reduction of its double bond, which is the one present in rotenone, to dihydro-tubaic acid (II), $C_{12}H_{14}O_4$, m.p. 166° (*Takei*, *Koide* and *Miyajima*, Ber. **68**, 1372), corresponds to the conversion of rotenone into dihydro-rotenone, because the latter with alcoholic potash gives the same dihydro-tubaic acid. Just as rotenone can be reduced to dihydro-rotenonic acid, via rotenonic acid, tubaic acid can be reduced and the ring opened with Na amalgam to the corresponding isodihydro-tubaic acid (III), m.p. 166°, which is converted by catalytic hydrogenation into tetrahydro-tubaic acid (IV), $C_{12}H_{16}O_4$, m.p. 206° (diacetate m.p. 143°) (*Takei*, *Miyajima* and *Ono*, Ber. **64**, 1000; *Haller* and *La Forge*, Am. **54**, 1988):



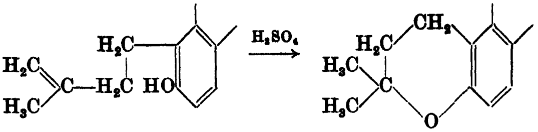
This series of reactions takes place with all derivatives of rotenone which contain the tubaic acid residue unchanged; e.g. with rotenol (idem, Ber. **65**, 279), rotenonic acid (idem, ibid. 1041), derrisic acid (*Takei*, *Koide* and *Miyajima*, Ber. **68**, 1370; *Takei*, *Miyajima* and *Ono*, Ber. **64**, 248, 1000) and derritol (idem, ibid.). Tubaic acid and its reduction products, which have been shown to be derivatives of resorcinol by fusion with potash (idem, ibid.), can be decarboxylated to the corresponding tubanols (tubanol, $C_{11}H_{12}O_2$, liquid; dihydrotubanol, m.p. 58°; tetrahydrotubanol, m.p. 85°); the carbon skeleton in these compounds has been established by the synthesis of tetrahydro-tubanol (2:6-dihydroxy-isoamyl-benzene) from 2:6-dimethoxy-benzonitrile and isobutyl-magnesium-bromide (*Haller*, Am. **54**, 4755).

The presence of the terminal double bond in the side chain is confirmed (**a**) by ozonolysis of acetyl-tubaic acid, $C_{14}H_{14}O_5$, to the acetate of the keto-carboxylic acid $C_{18}H_{12}O_6$, m.p. 145° (*Kariyone*, *Kondo* and *Makabe*, J. Pharm. Soc. Japan **48** (1928), 87; *Takei* and *Koide*, Ber. **62**, 3030; *Haller* and *La Forge*, Am. **53**, 4460), and (b) by ozonolysis of the methyl ether of tubanol, $C_{12}H_{14}O_2$, m.p. 116–117°, with the loss of one C-atom to a methyl ketone methyl ether, $C_{11}H_{12}O_3$, b.p. 126–127°/7 mm. (*Takei* and *Koide*, Ber. **62**, 3030), which with iodine and alkali yields the acid, $C_{10}H_9O_4I$, m.p. 140°. Permanganate oxidation of tubaic acid gives tubadiolic acid $C_{12}H_{14}O_6$, m.p. 201° (*Takei*, *Miyajima* and *Ono*, Ber. **65**, 279). The side-chain of the phenolic nucleus, cyclised in tubaic acid to a hydrofuran ring, has been isolated as isobutyl-acetic acid by oxidising tetrahydro-tubaic acid with $KMnO_4$ (*Takei*, *Koide* and *Miyajima*, Ber. **63**, 1372; **65**, 1041); dihydro-tubaic acid under the same treatment gives isobutyric acid, and the isopropenyl group of tubaic acid appears as acetic acid (*Takei* and *Koide*, Ber. **62**, 3030).



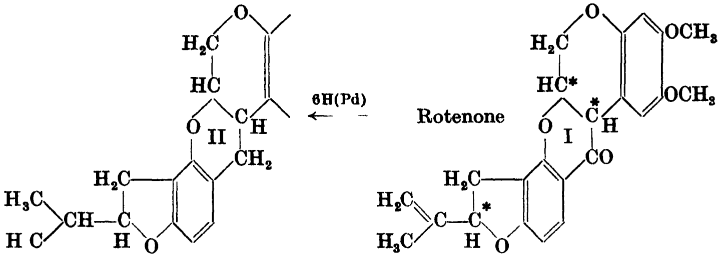
The terminal double bond of tubaic acid migrates into the ring under the influence of conc. H_2SO_4 or by potash fusion, giving isotubaic acid (rotenic acid), $C_{12}H_{12}O_4$, m.p. 184° (*Takei*, *Koide* and *Miyajima*, Ber. **63**, 508); its constitution is proved by degradation to isotubanol (roteol), $C_{11}H_{12}O_2$, m.p. 60°, resorcinol and isovaleric acid (idem, ibid. 1369; *Takei*, *Miyajima* and *Ono*, Ber. **64**, 1000), and to isobutyric acid (*Butenandt* and *Hildebrandt*, Ann. **477**, 253). It has been synthesised from 5-isopropyl-furfural and sodium succinate, by treating the isotubanol formed with CO_2 and Na methoxide, and hence it must be 2-isopropyl-4-hydroxy-coumarone-5-carboxylic acid (*Reichstein* and *Hirt*, Helv. 1933, **16**, 121). The furan ring is considerably more stable to Na amalgam, and the double bond is more difficult to reduce than with tubaic acid; the centre of asymmetry which is lost in its formation appears again when it is reduced to dihydro-rotenic acid, $C_{12}H_{14}O_4$, m.p. 166°, which is identical with dihydro-tubaic acid (formula II, p. 504). This type of isomeric change (cf. *Butenandt* and *Hildebrandt*, Ann. **477**, 245) also takes place with rotenone and its derivatives, e.g. with rotenol (*Haller* and *La Forge*, Am. **53**, 2271), dehydro-rotenone, derrisic acid, and derritol (*La Forge*, *Haller* and *Smith*, Am. **53**, 4400); this is further support for the presence of the tubaic acid residue in the rotenone molecule. Similarly, the action of sulphuric and acetic acids on rotenone gives isorotenone, $C_{23}H_{22}O_6$, m.p. 178° (*Takei*, Biochem. Z. **157**, 4; Ber. **61**, 1003; *Takei*, *Miyajima* and *Ono*, Ber. **64**, 1000; *Butenandt* and *Hildebrandt*, Ann. **477**, 248), which yields the inactive rotenic acid with alcoholic potash; the latter is also formed directly by fusion of rotenone with potash.

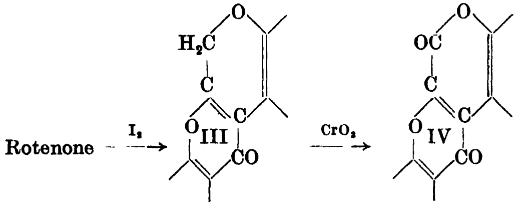
Another striking rearrangement which is also brought about by conc. H_2SO_4 is that of rotenonic acid, $C_{23}H_{24}O_6$, (in which the furan ring is opened) to β-dihydro-rotenone, m.p. 156° (*Haller*, Am. **53**, 733; *Takei*, *Miyajima* and *Ono*, Ber. **66**, 479, 1826). This also involves the tubaic acid half of the rotenone molecule, and a pyran ring is formed (cf. deguelin, p. 509).



In view of the fact that the fundamental hydrocarbon of rotenone, $C_{21}H_{26}$, contains one double bond and has 18 H-atoms less than the aliphatic hydrocarbon $C_{21}H_{44}$, it is highly probable that the molecule contains two aromatic nuclei.

The action of H_2O_2 on certain characteristic derivatives of rotenone makes it possible to settle the nature of the second half of the molecule and also how it is united with the tubaic acid component which is unattacked by H_2O_2. The constitution of rotenone itself (I) can be deduced from those of these derivatives and is shown below.

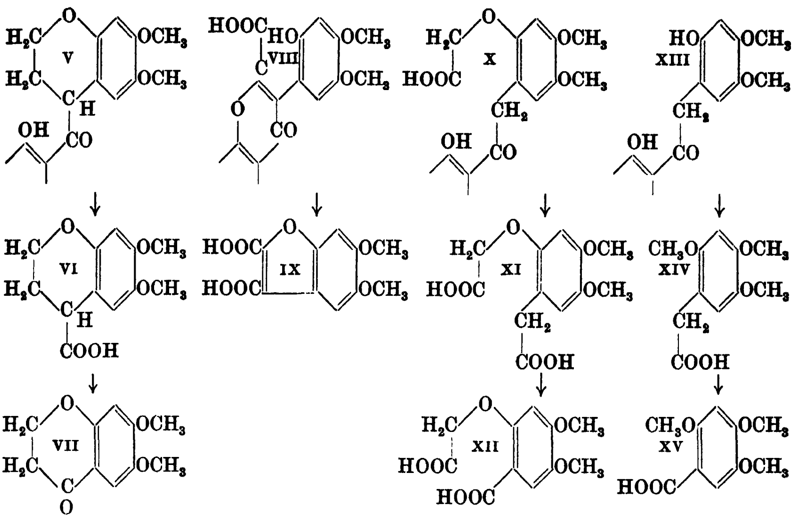




This formula is in complete agreement with the reactions of the tubaic acid residue already described, such as the formation of dihydro-rotenone, rotenonic acid, dihydro-rotenonic acid, isorotenone and β-dihydrorotenone. Dihydro-desoxy-rotenone has formula (II).

With iodine and potassium acetate or with air and alkali, rotenone gives two stereoisomeric rotenolones, $C_{23}H_{22}O_7$, m.ps. 141° and 210° (oxime m.p. 175°, see *La Forge* and *Smith*, Am. **52**, 3603; *La Forge* and *Haller*, Am. **56**, 1620; *Takei*, *Miyajima* and *Ono*, Ber. **66**, 479), which readily lose water with alcoholic sulphuric acid to give the yellow dehydro-rotenone (III), $C_{23}H_{20}O_6$, m.p. 224°; this compound has lost the two adjacent centres of asymmetry (*Takei*, Biochem. Z. **157**, 13; *La Forge* and *Smith*, Am. **52**, 1091; *Takei*, *Miyajima* and *Ono*, Ber. **64**, 248; **65**, 1041), and can also be prepared by direct dehydrogenation of rotenone with iodine. Further oxidation with CrO_3 or HNO_2 attacks the methylene group which is activated by the adjacent double bond, and gives a doubly unsaturated deep yellow diketone, rotenonone (IV), $C_{23}H_{18}O_7$, m.p. 298° (*Butenandt*, Ann. **464**, 257).

If rotenone is reduced with Zn and alkali the γ-pyrone ring of rotenone is opened and the product is rotenol (V, below), $C_{23}H_{24}O_6$, m.p. 121° (idem, ibid. 258; *La Forge* and *Smith*, Am. **52**, 1088; *Takei*, *Miyajima* and *Ono*, Ber. **65**, 279); its oxidation with H_2O_2 yields tubaic acid and netoric acid (VI), $C_{12}H_{14}O_5 \cdot H_2O$, m.p. 92°, anhyd. m.p. 131° (see idem, ibid.), which has been synthesised (*Robertson* and *Rusby*, J. **1936**, 212).

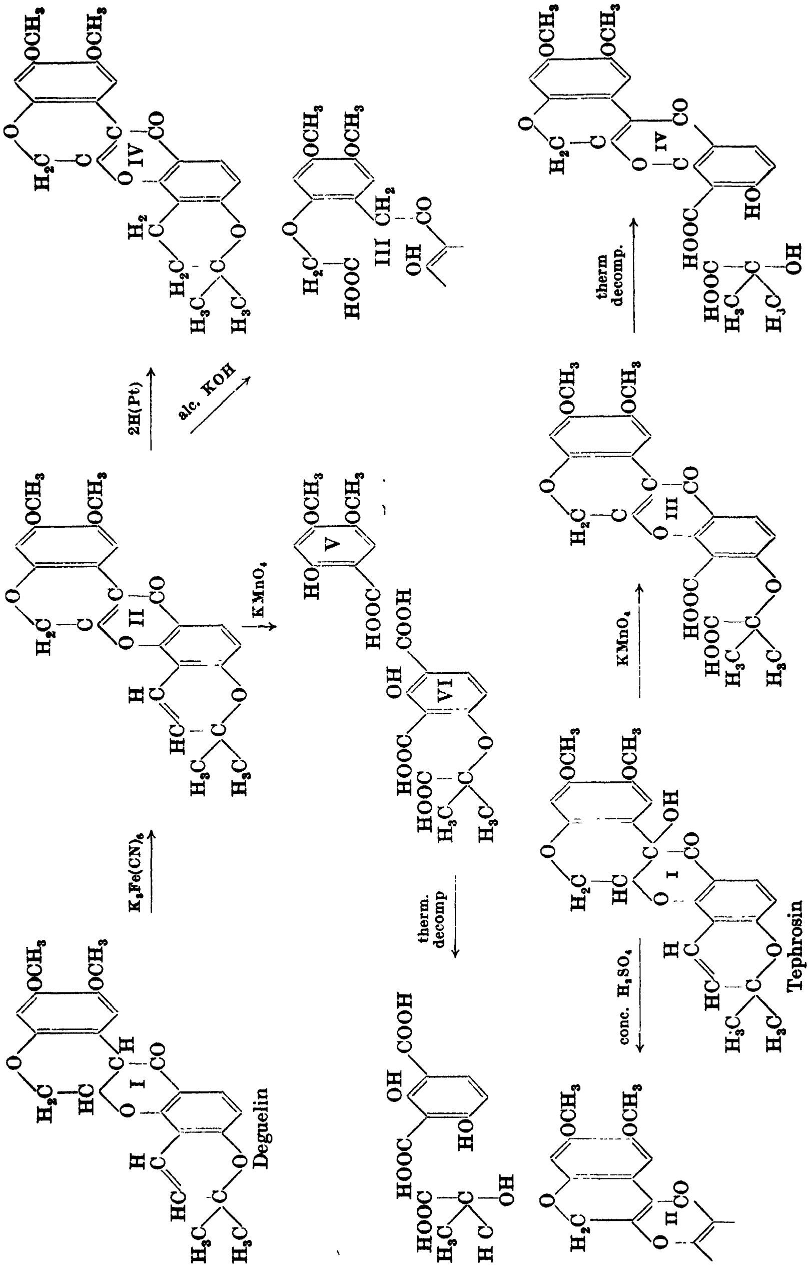


Netoric acid is oxidised by permanganate to the ketone (VII), $C_{11}H_{12}O_4$, m.p. 121° (6:7-dimethoxy-benzo-2:3-dihydro-γ-pyrone). Similarly, rotenone is oxidised by alkaline H_2O_2 to dehydro-netoric acid (toxicaric acid, see p. 510), $C_{12}H_{12}O_5$, m.p. 212°, probably via the tautomeric dehydro-rotenol (*Butenandt* and *Hilgetag*, Ann. **506**, 158).

Alcoholic potash opens the α-pyrone ring of the rotenonone molecule, which is the less stable, giving rotenononic acid (VIII), $C_{23}H_{20}O_8$, m.p. 250° (*Takei*, Biochem. Z. **157**, 6; *Butenandt*, Ann. **464**, 258; *Butenandt* and *McCartney*, Ann. **494**, 17); this is degraded by H_2O_2 to tubaic acid and abutic acid (IX), $C_{12}H_{10}O_7$, m.p. 264° (*Takei, Miyajima* and *Ono*, Ber. **65**, 1041).

Hydrolysis of dehydro-rotenone, which has been mentioned already, opens both condensed oxygen rings to give derrisic acid (X), $C_{23}H_{24}O_8$, m.p. 152° (*Butenandt*, Ann. **464**, 261; *Butenandt* and *Hildebrandt*, Ann. **477**, 249; *Takei, Miyajima* and *Ono*, Ber. **64**, 248). This compound has been identified by oxidation with H_2O_2 or $KMnO_4$ (*Takei, Koide* and *Miyajima*, Ber. **63**, 1370; *Takei, Miyajima* and *Ono*, Ber. **64**, 248, 1000; *Butenandt* and *McCartney*, Ann. **494**, 17) to tubaic acid and derric acid (XI), $C_{12}H_{14}O_7$, m.p. 171° (dimethyl ester m.p. 66°), and conversion of the latter into risic acid (XII), $C_{11}H_{12}O_7$, m.p. 262° (dimethyl ester m.p. 84°), and decarboxy-risic acid, $C_{10}H_{10}O_5$, m.p. 116° (methyl ester m.p. 45°) (see *La Forge* and *Smith*, Am. **52**, 2878; *La Forge*, Am. **53**, 3896). Both derric acid (*Robertson*, J. **1934**, 1380) and risic acid (idem, ibid.; *Takei, Miyajima* and *Ono*, Ber. **65**, 1042) have been prepared synthetically.

When rotenone is treated with Zn and alkali, in addition to the formation of rotenol, an interesting and typical fission takes place: two carbon atoms are lost, possibly as acetaldehyde, giving derritol (XIII), $C_{21}H_{22}O_6$, m.p. 161° (*Butenandt*, Ann. **464**, 259), which can be obtained in another way from rotenonone by hydrolysis with alcoholic KOH, oxalic acid being lost. The enol form of derritol is converted by distillation in a high vacuum into a furan derivative, anhydro-derritol, $C_{21}H_{20}O_5$, m.p. 160° (*Smith* and *La Forge*, Am. **54**, 2996). Oxidation of derritol methyl ether gives tubaic acid, while the methoxylated component is isolated as homo-asaronic acid (XIV), $C_{11}H_{14}O_5$, m.p. 93°; $KMnO_4$ converts this into asaronic acid (XV), $C_{10}H_{12}O_5$, m.p. 143°, which is 2:4:5-trimethoxy-benzoic acid (idem, Am. **52**, 4595; **53**, 3072; *Takei, Miyajima* and *Ono*, Ber. **64**, 1000; **65**, 279).


Deguelin
I
$K_3Fe(CN)_6$
II
2H(Pt)
IV
alc. KOH
III
$KMnO_4$
V
VI
therm. decomp
Tephrosin
I
conc. H_2SO_4
II
$KMnO_4$
III
therm decomp.
IV

The synthesis of rotenone derivatives has been carried out from synthetic homo-asaronic acid and tetrahydro-tubaic acid via tetrahydro-derritol methyl ether (idem, Ber. **65**, 1041), which is condensed with oxalic ester to rotenonone (idem, ibid.), or with bromacetic ester to give derrisic acid (*La Forge, Haller* and *Smith*, Am. **53**, 4400), which is cyclised to dehydro-rotenone (*Takei, Miyajima* and *Ono*, Ber. **65**, 1041).

Experiments on the toxicity of rotenone and its derivatives show that 0·00001% of rotenone and 0·0001% of hydrorotenone are poisonous, while isorotenone is almost without action. Experiments have also been carried out with some of the acid derivatives, which are active at the following concentrations: 0·0005% rotenic acid, 0·001% hydrotubaic acid, 0·005% of tubaic acid (*Takei, Koide* and *Miyajima*, Ber. **63**, 511, 1371; cf. *Gersdorff*, Am. **52**, 5051). The toxicity of the natural products which accompany rotenone is for toxicarin 65%, for deguelin 56%, and for tephrosin 23% of the activity of rotenone (*Gersdorff*, Am. **53**, 1897).

Deguelin (I, p. 508), $C_{23}H_{22}O_6$, m.p. 171°, is found as a constituent of several tropical plants poisonous to fishes, e.g. in derris and cube roots, in the leaves of *Cracca* (*Tephrosia*) *Vogelii* and *toxicaria* (*Clark*, Science **71** (1930), 396; Am. **52**, 2461; *Butenandt* and *McCartney*, Ann. **494**, 17; *Butenandt* and *Hilgetag*, Ann. **495**, 172).

Like the isomeric rotenone, deguelin can be oxidised with potassium ferricyanide to dehydro-deguelin (II), $C_{23}H_{20}O_6$, m.p. 233°, which is converted by alcoholic potash into deguelinic acid (III), $C_{23}H_{24}O_8$, m.p. 189°, analogous to derrisic acid (*Clark*, Am. **53**, 313). The methoxylated aromatic component is the same as in rotenone, since oxidising agents such as H_2O_2 give derric acid, $C_{12}H_{14}O_7$, m.p. 171° (see above; *Butenandt*, Ann. **464**, 253; *Clark*, Science **73** (1931), 17), and $KMnO_4$ yields risic acid, $C_{11}H_{12}O_7$, m.p. 262° (see above; *Clark*, Am. **53**, 2369).

The constitution of the half of the molecule which corresponds to tubaic acid in rotenone was disclosed by the catalytic reduction of dehydro-deguelin to dihydro-dehydro-deguelin (IV), $C_{23}H_{2}O_6$, m.p. 267° (idem, ibid.). This compound was found to be identical with dehydro-β-dihydro-rotenone, in which the hydrofuran ring of the tubaic acid acid component is enlarged to a pyran ring (*Clark*, Am. **53**, 729; cf. also *Takei, Miyajima* and *Ono*, Ber. **66**, 1826). Dehydro-deguelin can be oxidised with CrO_3 to dehydro-deguelone, $C_{23}H_{18}O_7$, a yellow compound m.p. 292°, the analogue of rotenonone.

Oxidation of dehydro-deguelin with permanganate gives both aromatic components: 2-hydroxy-4:5-dimethoxy-benzoic acid (V), $C_9H_{10}O_5$, m.p. 213° (*Clark*, Am. **53**, 2007, 3431), and niconic acid (VI), $C_{12}H_{18}O_8$, m.p. 196° (idem, Am. **54**, 3000). When heated, the latter gives α-hydroxy-isobutyric acid, m.p. 79°, and 2:6-dihydroxy-phthalic acid, m.p. 162°.

These reactions and the relationship of deguelin to rotenone are shown in the formulae on p. 508.

Tephrosin, *hydroxy-deguelin,* (I) (p. 508, bottom row), $C_{23}H_{22}O_7$, m.p. 198°, is found with rotenone, deguelin and toxicarin in derris and cube roots, and with deguelin in the leaves of *Cracca* (*Tephrosia*) *Vogelii* (*Clark*, Science **73** (1931), 17).

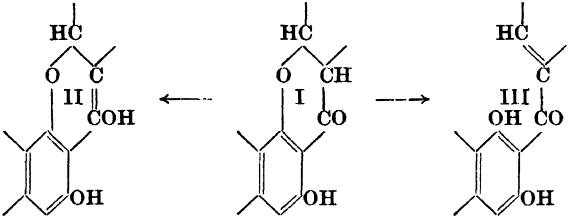
Its constitution could be established with comparative ease because it is converted by sulphuric and acetic acids into dehydro-deguelin (II), $C_{23}H_{20}O_6$, m.p. 233°; this process is similar to the dehydration of rotenolone to dehydro-rotenone. The reactive double bond of tephrosin is shown to be in the ring by the oxidation with permanganate to two isomeric yellow tephrosin-dicarboxylic acids (III), $C_{23}H_{22}O_{11}$, m.ps. 221° and 177° (*Clark*, Science **71** (1930), 396; Am. **53**, 729), which in boiling diphenyl ether break down to α-hydroxy-isobutyric acid and tephrosin-monocarboxylic acid (IV), $C_{19}H_{14}O_8$, m.p. 269° (see *Clark*, Am. **54**, 3000; cf. formulae on p. 508).

Hydrolysis of tephrosin-di- and -monocarboxylic acids opens simultaneously both of the remaining oxygen rings in the molecule (*Clark*, Am. **55**, 759), and corresponds to the conversion of dehydro-rotenone into derrisic acid (cf. under rotenone).

Tephrosin is often accompanied by a stereoisomer, **isotephrosin**, m.p. 252° (*Clark* and *Claborn*, Am. **54**, 4454). Since both isomers are dehydrated to the same dehydro-deguelin, m.p. 233° (*Clark*, Am. **53**, 729), the isomerism of tephrosin and isotephrosin seems to be similar to that of the rotenolones obtained from rotenone and iodine, and probably arises from the hydration of the dehydro-compound in two directions (*Clark* and *Claborn*, loc. cit.).

The conclusion that tephrosin and its isomer are hydroxy-deguelins finds further support in their formation from deguelin by atmospheric oxidation in alkaline solution (*Takei*, *Miyajima* and *Ono*, Ber. **66**, 1826).

Toxicarol (I), $C_{23}H_{22}O_7$, m.p. 220°, the chief poisonous constituent of the South American plant *Cracca* (*Tephrosia*) *toxicaria*, is a fish-poison and is also found with rotenone in derris and cube roots. It is an isomer of tephrosin. While the latter compound is a hydroxy-derivative of deguelin of the rotenolone type, toxicarol has the hydroxyl on the methoxyl-free aromatic nucleus. This makes it difficult to identify the carbonyl group in the adjacent γ-pyrone ring (I), and also causes the compound to enolise very readily; the free enol form (II), m.p. 160–170°, can be isolated from the diacetate, m.p. 236°. A further consequence is that the ring opens readily with alkali to the tautomeric, optically inactive form (III) (monoacetate, m.p. 182·5°):

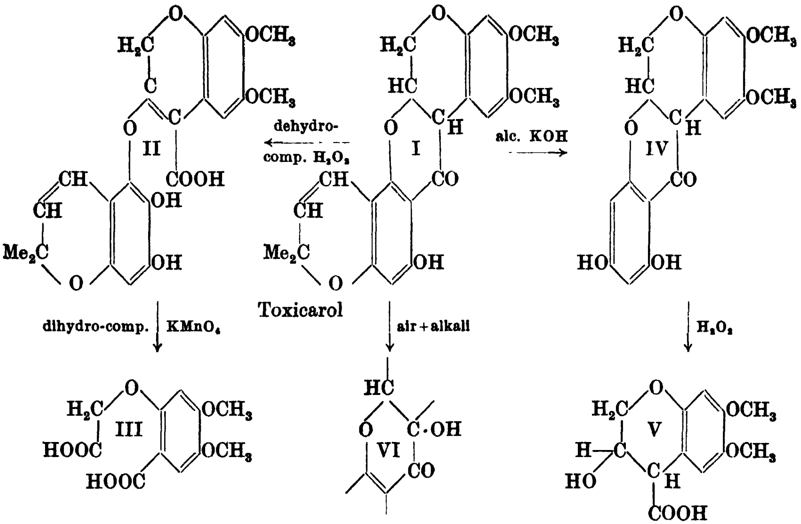


In the reactions of both the condensed oxygen-rings toxicarol closely resembles rotenone, deguelin and tephrosin. For example, it can be degraded via dehydro-toxicarol, $C_{23}H_{20}O_7$, m.p. 234° (monoacetate m.p. 236°, see *Clark*, Am. **52**, 2461; **53**, 2264; *Butenandt* and *Hilgetag*, Ann. **495**, 176), and toxicarolic acid, $C_{23}H_{24}O_9$, to risic acid, $C_{11}H_{12}O_7$, m.p. 262° (see pp. 507, 511) (*Clark*, Am. **54**, 1600), and with nitrous acid it gives toxicarolone, $C_{23}H_{20}O_8$, m.p. 284° (*Butenandt* and *Hilgetag*, Ann. **495**, 176). The double bond which can be hydrogenated is in the side-chain of the second aromatic component, as in rotenone, and the keto-group of dihydro-toxicarol, $C_{23}H_{24}O_7$, m.p. 209° (diacetate m.p. 240°; see *Clark*, Science **71** (1930), 396) can be reduced to form dihydro-desoxy-toxicarol, $C_{23}H_{26}O_6$, m.p. 188° (monoacetate m.p. 156°, see *Clark*, Am. **53**, 2264). This side chain has been shown to be present as a dimethyl-chromen ring, as in deguelin (*Bridge*, *Hayes* and *Robertson*, J. **1937**, 279; *George* and *Robertson*, ibid. 1535).

The influence of the phenolic hydroxyl in the ortho-position to the carbonyl is shown, however, in the ease with which the γ-pyrone ring of dehydro-toxicarol is opened by H_2O_2 to dehydro-toxicarol-carboxylic acid (II, p. 511), m.p. 230°; oxidation of the dihydro-compound of the latter yields as final product risic acid (III), $C_{11}H_{12}O_7$, m.p. 262° (*Clark*, Am. **54**, 1600).

The phenolic hydroxyl appears to be of particular significance for a characteristic abnormal reaction of toxicarol with alcoholic KOH, which splits off the C_5 chromen ring and gives apotoxicarol (IV), $C_{18}H_{16}O_7$, m.p. 247° (triacetate m.p. 206°) (*Clark*, Am. **54**, 2537). Further oxidation of the latter gives hydroxy-netoric acid (V), $C_{12}H_{14}O_6$, m.p. 189°, and its dehydration product, dehydro-netoric acid (toxicaric acid), $C_{12}H_{12}O_5$, m.p. 212°, which can be reduced to netoric acid, $C_{12}H_{14}O_5$, m.p. 87° and 131° (idem, ibid.). The constitution of these three acids has been confirmed by their synthesis (*Robertson* and *Rusby*, J. **1936**, 212).

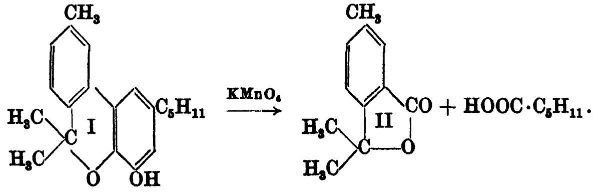
Just as deguelin can be converted into tephrosin, toxicarol, which is hydroxy-deguelin, undergoes atmospheric oxidation in presence of alkali to 7-hydroxy-toxicarol (VI), $C_{32}H_{22}O_8$, m.p. 227° (*Clark*, Am. **56**, 987).



The active principle of hashish, from Indian hemp, *Cannabis indica*, is **cannabinol** (I), $C_{21}H_{26}O_2$, b.p. 263–264°/20 mm., $[\alpha]_D - 108°$, which is a narcotic with an action similar to that of opium (*Schneider*, J. Amer. Pharm. Assoc. **12** (1923), 208).

The compound is phenolic (methyl ether m.p. 66°; acetate m.p. 75°, see *Cahn*, J. **1931**, 630), and the difficulty of methylation of the hydroxyl indicates that it is next to the second oxygen atom, which forms part of a ring (*Cahn*, J. **1932**, 1342). $KMnO_4$ oxidises away the phenolic part of the molecule and gives n-caproic acid and cannabinolactone (II), $C_{11}H_{12}O_2$, b.p. 156°/16 mm. (*Bergel*, Ann. **482**, 55; *Cahn*, J. **1930**, 986). The constitution of the latter was established by its conversion into cannabinolactonic acid, $C_{11}H_{10}O_4$, m.p. 205° (by oxidation of CH_3 to COOH), and trimellitic acid, m.p. 220° (*Cahn*, J. **1932**, 1342), and also by potash fusion to m-toluic acid and isophthalic acid; it has been confirmed by its synthesis (*Bergel* and *Vögele*, Ann. **493**, 250). The dinitro-cannabinol, $C_{21}H_{24}O_6N_2$, m.p. 183°, obtained from the methyl ether of cannabinol, is nitrated in the phenolic nucleus by nitric acid in acetic acid to give trinitrocannabinol, $C_{21}H_{23}O_8N_3$, m.p. 160°, because the methyl ether, m.p. 150°, of the latter can be degraded with conc. HNO_3 to dinitro-cannabinolactone, $C_{11}H_{10}O_6N_2$, m.p. 161° (*Cahn*, J. **1931**, 630).

The whole molecule contains 21 C-atoms, of which eleven are in the skeleton of cannabinolactone, while six are isolated as caproic acid. Hence it follows that the carbonyl groups in each of degradation products arise from the oxidation of the phenolic component; this is shown in the following tentative formulae:



The action of HCl in acetic acid at a high temperature on acetyl-cannabinol leads to the loss of the isopropyl group and the formation of 3-methyl-5′-amyl-2′:3′-dihydroxy-diphenyl, $C_{18}H_{22}O_2$, m.p. 62° (*Cahn*, J. **1933**, 1400).

Complex Carbocylic Ring Systems

This group includes the many saponins, which are widely distributed in nature, and the toad-poisons.

e) THE SAPONINS

The saponins are plant substances with a marked tendency to form foams (their name is derived from *sapo*, soap); they mostly contain sugars, and their aglycones, the "sapogenins", are derived from polycyclic ring systems. They give characteristic colour reactions with conc. sulphuric acid, acetic anhydride, etc., and many give difficultly soluble molecular compounds with sterols (e.g. cholesterol, see *Windaus*, Ber. **42**, 238; Z. physiol. Chem. **65**, 110; *Riesenfeld* and *Lummerzheim*, ibid. **87**, 270; *Halberkann*, *Biochem. Z.* **19**, 310; *Kofler* and *Raum*, ibid. **219**, 335), and with phenols and alcohols (*Windaus* and *Weinhold*, Z. physiol. Chem. **126**, 299).

The saponins are remarkable for the many kinds of physiological activity which they possess. One of their most striking properties is their haemolytic action (for their detection in plants see *Fischer*, Mo. **56**, 282), which was shown by *Ransom* (1901) to be increased by cholesterol (*Kofler* and *Schrutka*, Biochem. Z. **159**, 327); according to *Windaus* (Ber. **42**, 238; *Ruzicka* and *van Veen*, Z. physiol. Chem. **184**, 73) this phenomenon depends upon the complex formation mentioned above (see *Schulman* and *Rideal*, Proc. Roy. Soc. B. **122**, 29).

The intensity of haemolysis runs parallel to their irritating effect on the eyes, to their taste and to their toxic effect on fish (*Kofler* and *Schrutka*, Biochem. Z. **159**, 327), as is shown in the table:

	Haemolysis limit		Haemolysis limit
Thea-saponin	1:1,000,000	Aesculin	1:50,000
Cyclamin	1: 400,000	Hederagin	1:50,000
Primulic acid	1: 190,000	Glycyrrhizin	1: 4,000
Senegin	1: 60,000		

	Eye Irritation	Taste	Fish Index
Digitonin	230,000	380,000	200,000
Primulic acid	110,000	250,000	36,000
Sapindus saponin	3,500	200,000	10,000
Aesculin	1,000	130,000	1,800
Gypsophila saponin	900	80,000	580

The saponins are fatal to various lower animals such as trypanosomes, paramaecians, etc. Tubercle bacilli lose their stability to acids (Z. Bact. **89**, I, 154; *Wyss*, C. r. **177**, 719), but other bacteria are to some extent aided in their development. Saponins catalyse the fermentation of sugar by yeast, but in the presence of the salts of uni- and divalent cations they hinder or prevent this process (*Boas*, Biochem. Z. **117**, 177; **129**, 144). They also have an important influence on other enzymes: e.g. they promote the action of urease and the hydrolysis of fats by pancreas lipase, but hinder the action of ricinus lipase. The destructive action of pepsin and trypsin upon insulin is checked by the saponins (*Lasch* and *Brugel*, ibid. **181**, 109), while rennin inactivated by charcoal regains its original activity in their presence (*Jahnson-Blohm*, Z. physiol. Chem. **82**, 178).

The saponins are used to produce foams in fire-extinguishers, and as mild, non-alkaline detergents. Plant extracts containing saponins are used medicinally as expectorants.

To isolate the saponins, the fat is first removed from the plant material and the residue extracted with water or alcohol. Enzymatic hydrolysis often takes place at this stage, so that the actual saponin (glycoside) can only be isolated under special conditions (*Stoll* and *Kreis*, C. 1933, II 1878; *Stoll*, *Kreis* and *Hofmann*, Z. physiol. Chem. **222**, 24). They can often be purified by means of their Ba, Mg and Pb salts, or by precipitation with tannic acid, or dialysis (*Kofler* and *Wolkenburg*, Biochem. Z. **160**, 398).

The ease with which the saponins are hydrolysed into the sapogenins and sugar varies; in some cases treatment with organic acids is sufficient (*Winterstein* and *Blau*, Z. physiol. Chem. **75**, 410), but usually 5—10% mineral acid is necessary, while a few must be heated in an autoclave. Sometimes hydrolysis can be carried out with enzymes (*Back*, Biochem. Z. **86**, 223), while another process uses oxidative fission with H_2O_2 (*Winterstein*, Z. physiol. Chem. **199**, 25; Germ. Pat. 275,048). Glucose, rhamnose and xylose have been isolated as the sugar components, and it has been shown that in general the hexoses are more readily eliminated than the pentoses.

Determination of the constitution. In many cases the action of oxidising agents breaks down the carbon ring-system. Distillation with Zn dust gives various hydrocarbons (*van der Haar*, Ber. **55**, 1054; Rec. **43** (1924), 542), but here, as in other cases, selenium is a much better dehydrogenating agent than Zn (*Ruzicka* and *van Veen*, Z. physiol. Chem. **184**, 69; *Ruzicka*, *Huyser*, *Pfeiffer* and *Seidel*, Ann. **471**, 21; *Ruzicka* and *van Veen*, Rec. **48** (1931), 1018). On such treatment some of the saponins and their derivatives give the hydrocarbon sapotalene, (1:2:7-trimethyl-naphthalene, picrate m.p. 131·5°, styphnate m.p. 160°, see *Späth* and *Homolka*, Mo. **60**, 117; *Ruzicka*, *Hosking* and *Wick*, Helv. **14**, 811; *Ruzicka* and *Ehmann*, Helv. **15**, 141); this compound is also obtained from members of other groups of compounds, such as the resin acids (abietic acid, elemic acid, p. 349 etc.) and the pentacyclic triterpene alcohols, such as amyrin, betulin, lupeol (p. 338), etc. (*Ruzicka* and *van Veen*, Z. physiol. Chem. **184**, 69; *Winterstein* and *Wiegand*, ibid. **199**, 46; *Winterstein* and *Hammerle*, ibid. 56; *Winterstein* and *Egli*, ibid. **202**, 207; *Winterstein* and *Stein*, ibid. 222; *Ruzicka* and collaborators, Helv. **15**, 431, 1496). A second group of saponins is dehydrogenated by Se to "Diels' hydrocarbon", $C_{18}H_{16}$, 3-methyl-cyclopentenophenanthrene, which shows the presence of the tetracylic cholane skeleton (*Jacobs* and *Simpson*, Am. **56**, 1424; J. Biol. Chem. **105** (1934), 501).

The saponins can therefore be divided into two classes[1]: (1) those which give sapotalene, i.e. the triterpenoid group, such as aesculin, boswellinic acid, camellia saponin, cyclamin, glycyrrhizin, gypsophila saponin, hederin, oleanolic acid, quillaic, sia- and suma-resinolic acids, ursolic acid, etc., (2) the saponins of the cholane group: tigonin, gitonin, digitonin and sarsaponin (parillin).

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[1] See *R. Tschesche*, Chemie der pflanzlichen Herzgifte, Krötengifte und Saponine der Cholangruppe: Ergebn. d. Physiol. **38** (1936), 31.

I. Saponins of the Triterpenoid Group

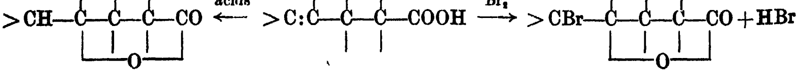
Several of the sapogenins derived from the saponins of this group are known to be closely related to one another, while with others the precise interrelationships have not yet been established, although the products they give on dehydrogenation show that they belong to the triterpene class. The compounds about which we have the most detailed knowledge are hederagenin, oleanolic acid and gypsogenin, and for these the main carbon skeleton and the positions of most of the reactive groups has been established, mainly owing to the work of *Ruzicka* and of *Kitasato.* These three compounds will be described first and their constitution discussed in detail; then the other members of the group will be mentioned more shortly.

Hederin (aralin, sapindus- or kalo-saponin), $C_{41}H_{64}O_{11}$, m.p. 256°, is a characteristic constituent of the *Araliaceae* group, such as ivy, *Hedera helix* (*van der Haar,* Arch. Pharm. **250** (1912), 424; **251** (1913), 632), *Aralia japonica* (*Winterstein* and *Stein,* Z. physiol. Chem. **211,** 5), *Kalopanax ricinifolius* (*Kotake* and *Taguchi,* C. 1932 I 2332), and of certain species of *Sapindus,* such as *Sapindus mukorossi* (*Winterstein* and *Meyer,* Z. physiol. Chem. **199,** 37; *Kitasato* and *Sone,* Acta phytochim. **6** (1932), 179). Acid hydrolysis of the saponin gives rhamnose, arabinose and **hederagenin,** $C_{30}H_{48}O_4$ ($C_{31}H_{50}O_4$; idem, ibid. **7** (1933), 1), m.p. 331°, $[\alpha]_D + 70°$ (diacetate m.p. 175°; methyl ester m.p. 237°, see *van der Haar,* Ber. **54,** 3142; **55,** 1064; diacetylester m.p. 190°, see *Jacobs,* J. Biol. Chem. **63,** 621; *van der Haar,* Rec. **46** (1927), 28; *Kotake, Taguchi* and *Okamoto,* C. 1933 II 1879).

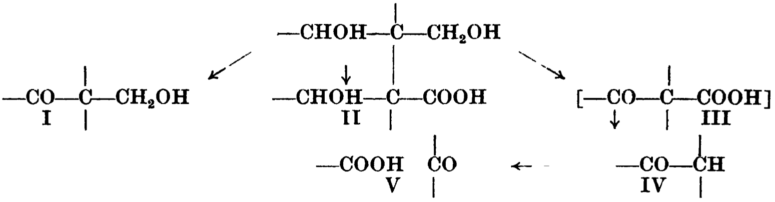
Oleanolic acid, $C_{30}H_{48}O_3$, m.p. 305°, $[\alpha]_D + 80°$, is one of the most widely distributed saponins (*Winterstein* and *Stein,* Z. physiol. Chem. **199,** 64; *Ruzicka* and collaborators, Helv. **15,** 431, 472). It is found in numerous plants, often combined with glucuronic acid (*van der Haar,* Rec. **46** (1927), 775), as in olive leaves (*Wedekind* and *Schicke,* Z. physiol. Chem. **198,** 181), in sugar beet, in cloves ("caryophyllin", see *Smolenski,* ibid. **71,** 266), in species of *Viscum* (*Winterstein* and *Hämmerle,* ibid. **199,** 56), in guaiac bark ("guagenin", see *van der Haar,* Biochem. Z. **76,** 335; *Wedekind* and *Schicke,* Z. physiol. Chem. **195,** 132), in *Panax repens* ("panaxin", see *Murayama* and *Itagaki,* J. Pharm. Soc. Japan **1923,** 53), and in species of *Aralia* (*van der Haar,* Ber. **55,** 3041; *Winterstein* and *Stein,* Z. physiol. Chem. **211,** 5), etc.

Gypsophila saponin (albasaponin, saponalbin) which occurs in *Gypsophila arrostii* and *panniculata* (*Bolley,* Ann. **90,** 211; *Kofler* and *Dafert,* Ber. **33,** 215) contains as aglycone **gypsogenin,** $C_{30}H_{46}O_4$, which sinters at 240° and melts at 268–271° (*Ruzicka* and *Giacomello,* Helv. **20,** 299). When treated with acetic anhydride, it gives two isomeric acetates; one, m.p. 176–177°, seems to be the true acetyl derivative of the secondary alcoholic group common to these sapogenins, while the other, m.p. 262°, is no longer a carboxylic acid like gypsogenin itself, and lactonisation must have taken place.

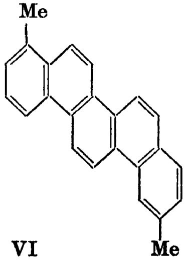
These three sapogenins all contain one carboxyl group, one double bond one secondary alcoholic group. The double bond is unreactive and is not attacked by catalytic reduction, but its presence is deduced from the fact that with strong mineral acids the compounds are converted into isomeric saturated lactones, while with bromine the product is a saturated bromolactone; thus hederagenin gives hederagenin-lactone, m.p. 355° (diacetate, m.p. 244°) and bromohederagenin-lactone, $C_{30}H_{47}O_4Br$, m.p. 288° (diacetate m.p. 233°), and oleanolic acid gives oleanolic lactone, m.p. 355°, and the bromolactone, $C_{30}H_{47}O_3Br$, m.p. 242° (*Winterstein* and *Meyer,* Z. physiol. Chem. **199,** 37; *Winterstein* and *Wiegand,* ibid. 46; *Winterstein* and *Stein,* ibid. 75). This has been taken to indicate that the double bond is in the $\gamma\delta$ position to the carboxyl group, though strict proof is lacking, and the formation of the lactones is held to take place as follows:



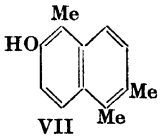
In addition to these groups, hederagenin contains a primary alcoholic group, gypsogenin is the related aldehyde containing CHO in place of CH_2OH, and oleanolic acid is the reduction product with CH_3 in place of CH_2OH. These important relationships are shown by the facts that gypsogenin semicarbazone gives oleanolic acid when heated with NaOEt (Wolff-Kishner reduction) and that gypsogenin is reduced catalytically to hederagenin (*Ruzicka* and *Giacomello*, Helv. **19**, 1136; **20**, 299). That gypsogenin is an aldehyde and not a ketone is confirmed by the fact that its acetyl bromolactone, $C_{32}H_{47}O_5Br$, m.p. 180–181°, in which the secondary alcoholic group is protected by acetylation, is oxidised by CrO_3 to an acid $C_{32}H_{47}O_6Br$, m.p. $> 310°$ (methyl ester m.p. 238–240°) (Idem, ibid.). The oxidation products of hederagenin confirm the presence of a primary alcoholic group, in addition to the secondary alcoholic group common to all the compounds, and establish the relative positions of the two hydroxyls. For example, when the methyl ester of hederagenin is oxidised with $KMnO_4$ (*Jacobs*, J. Biol. Chem. **68** (1925), 631) the methyl esters of a hydroxy-keto-acid $C_{30}H_{46}O_4$, m.p. 217–218° (I) and of a hydroxy-dicarboxylic acid $C_{30}H_{46}O_5$ (II), m.p. 274–276°, are formed, and must arise from the oxidation of the secondary and primary alcoholic groups respectively. Further oxidation of hederagenin methyl ester with CrO_3 (*Jacobs* and *Gustus*, ibid. **69** (1926), 641) gives a mixture of the esters of a keto-acid $C_{29}H_{44}O_3$, m.p. 208–210° (IV) and of a dibasic keto acid $C_{29}H_{44}O_5$, m.p. 161–163° (V). One carbon atom has been lost as CO_2, the typical behaviour of a β-ketonic acid (III).



The nature of the carbon skeleton to which these groups are attached is disclosed by dehydrogenation, coupled with the isoprene rule (p. 196), which states that the most probable structures are those which can be built up from isoprene units. Dehydrogenation of all the three sapogenins with Se or Pd (*Ruzicka* and co-workers, Ann. **471**, 25; Helv. **15**, 431, 1496; **17**, 442) gives the same products which include two important for the present argument: 1:8-dimethyl-picene $C_{24}H_{18}$ (VI), m.p. 304–306°, and 6-hydroxy-1:2:5-trimethyl-naphthalene (agathol) (VII). The first is important because it is a pentacyclic compound and the sapogenins are pentacyclic, as is shown by their formulae; hence identification of the picene settles the main carbon skeleton. This picene has been synthesised (*Ruzicka* and *Hofmann*, Helv. **20**, 1155) and its identity with the dehydrogenation product established beyond doubt. Hence the triterpene sapogenins contain five condensed rings arranged as in picene.



VI

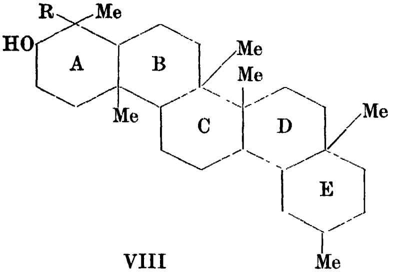


VII

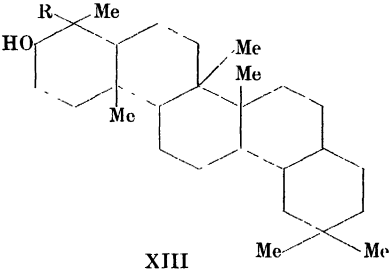
The hydroxy-trimethyl-naphthalene is important because it contains the hydroxy group which, as a secondary alcoholic group, is present in all the three sapogenins. The related methoxy compound has been synthesised (*Ruzicka*, *Hoffmann* and *Schellenberg*, Helv. **19**, 1391) and found to be identical with the methylated dehydrogenation product.

If we neglect for the moment the carboxyl group and the double bond present in the sapogenins and the characteristic primary alcoholic group of hederagenin which becomes an aldehyde group in gypsogenin, the remainder of the molecule must consist of groups which are lost on dehydrogenation, and from the isoprene rule these are almost certainly methyl groups. Further, since they are lost, they must be in angular positions. This leads to carbon skeletons of the type VIII (see p. 517).

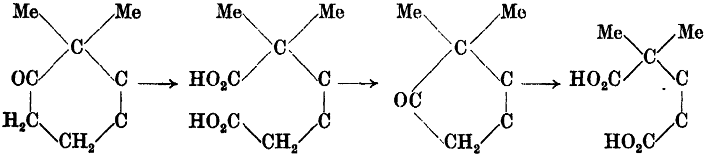
This represents a reduced picene structure with R the group which is CH_3 in oleanolic acid and CH_2OH in hederagenin, its relative position to the OH being settled by the oxidation results described above. Such a structure will account for the other dehydrogenation products, 1:2:3:4-tetramethylbenzene coming from ring A, 2:7-dimethyl-naphthalene and 1:2:7-trimethylnaphthalene (sapotalene) from rings D and E, 1:2:5:6-tetramethylnaphthalene from rings A and B with wandering of a methyl group, and 1:7:8-trimethyl-phenanthrene from rings A, B and C (*Ruzicka*, *Goldberg* and *Hofmann*, Helv. **20**, 325). This structure for rings A and B is not only supported by the oxidation results described above, but also by the more profound oxidations carried out by *Kitasato* and *Sone* (Acta phytochim. **7** (1933), 4; (1935), 66). Further the oxidation of betulin, a triterpene alcohol which presumably contains the same structure since it gives the same dehydrogenation products, provides full evidence for ring A (*Dischendorfer* and *Polak*, Mo. **51**, 43; *Ruzicka*, Helv. **17**, 428; **19**, 509). Dihydrobetulin with CrO_3 gives a ketonic acid (IX; the COOH is in another part of the molecule) which with HNO_3 gives a tribasic acid (X). This acid can be cyclised to a ketone (XI) which is oxidised to the acid (XII); the latter forms a stable anhydride and hence must be a glutaric acid.



VIII



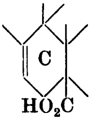
XIII

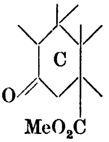


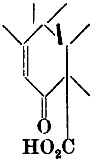
IX X XI XII

Structure VIII advanced by *Ruzicka* is not the only solution possible for rings C, D and E and *Kitasato* (Acta phytochim. **10** (1) (1937), 199) prefers a different distribution of methyl groups. Another possibility (XIII) has been suggested by *Haworth* (Ann. Rep. Chem. Soc. **34** (1937), 338).

There remains the question of the position of the double bond and the carboxyl group in hederagenin, gypsogenin and oleanolic acid. These were originally places in ring E because of the results obtained by *Schicke* and *Wedekind* (Z. physiol. Chem. **215**, 199) from the oxidation of acetyl oleanolic acid, in which the secondary alcoholic group is protected by acetylation. These results are, however, erroneous and the groups cannot be in a terminal ring (*Ruzicka* and *Cohen*, Helv. **20**, 1192). The double bond is very unreactive and the products formed in the oxidation of acetyl oleanolic acid and its derivatives are difficult to interpret consistently on any hypothesis. The first product obtained from the methyl ester of that compound ($C_{33}H_{52}O_4$) with H_2O_2 is $C_{33}H_{52}O_5$, m.p. 195–196°, which shows no ketonic or double bond reactions. It is not, however, the ether formed by addition of O to the double bond, because this compound is known. Its absorption spectrum with a maximum at 2900 Å shows that it is in fact a ketone (*Ruzicka* and *Cohen*, Helv. **20**, 804). Similarly the keto-acetyl-oleanolic acid $C_{30}H_{46}O_4$, m.p. 282–284° obtained by oxidation with CrO_3 (*Kitasato*, Acta phytochem. **7** (1933), 185; **9** (1935), 53, 69, 136, 323) has the absorption spectrum of an $\alpha\beta$-unsaturated ketone, but no ketonic or double bond reactions. *Ruzicka* places the double bond and carboxyl group in ring C, as in XIV, and formulates the two ketones mentioned as XV and XVI.

XIV 

XV 

XVI 

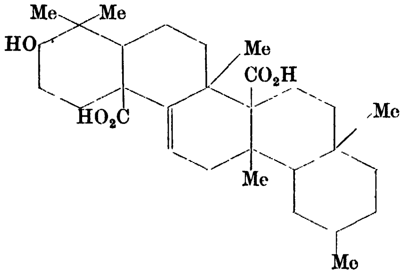
Kitasato (ibid. **10** (1) (1937), 199) and *Haworth* (loc. cit.) also place the double bond in ring C but suggest alternative positions for the carboxyl group. For a discussion of the further oxidation products of acetyl oleanolic acid and its derivatives see *Haworth*, Ann. Rep. Chem. Soc. **34** (1937), 333.

The liquorice root (*Glycyrrhiza glabra*) contains **glycyrrhizin** $C_{57}H_{92}O_{18}$ (?), m.p. 220 (*P. Karrer*, *W. Karrer* and *Chao*, Helv. **4**, 100; *Tocca*, C. 1924 II, 709, 2184). Hydrolysis of this saponin gives the sapogenin **glycyrrhetic acid** $C_{30}H_{46}O_4$ which has two crystalline forms, m.ps. 300–304° and 287–293°. It is a monohydroxy-monocarboxylic acid (methyl ester m.p. 259°) like oleanolic acid and on dehydrogenation gives sapotalene and 1:8-dimethylpicene (*Ruzicka* and co-workers, Helv. **20**, 312, 804). The fourth oxygen atom does not show ketonic reactions and the double bond is non-reactive, but the compound has an absorption spectrum with a maximum at 2550 Å, characteristic of $\alpha\beta$-unsaturated ketones, and hence the acid is almost certainly isomeric with keto-oleanolic acid. The presence of the group —CH:CH·CO— is shown by the reduction of the acid, its methyl ester and the acetyl derivative of the latter; in all cases the oxygen atom is replaced by two hydrogens to give desoxo compounds which show the yellow colour with $C(NO_2)_4$ characteristic of unsaturated compounds (*Ruzicka* and *Schellenberg*, Helv. **20**, 1271).

Chinovin, $C_{36}H_{56}O_9$, is a bitter substance from the false quinine bark of *China nova*, α-form $[\alpha]_D + 56°$, β-form from *Cuprea* bark, m.p. 235 , $[\alpha]_D + 29{\cdot}7°$ (*Hlasiwetz*, Ann. **79**, 145; *Liebermann* and *Giesel*, Ber. **16**, 926; *Oudemans*, Rec. **2** (1883), 163; *Rochleder*, J. pr. (1) **102** (1867), 16). It has the properties of a saponin and is hydrolysed by alcoholic HCl to **chinovic acid**, $C_{30}H_{46}O_5$, m.p. 298°, and chinovose, $C_6H_{12}O_5$ (*d*-ε-rhamnose, see *Fischer* and *Liebermann*, Ber. **26**, 2415; *Freudenberg* and *Raschig*, Ber. **62**, 373).

Chinovic acid is a monohydroxy-dicarboxylic acid; the hydroxyl is shown by benzoylation, and the carboxyls are probably attached to tertiary carbon atoms because of the difficulty of hydrolysis of its dimethyl ester, m.p. 174°. The acid loses CO_2 on heating to give the monocarboxylic pyro-chinovic acid $C_{29}H_{46}O_3$, m.p. 196° (methyl ester m.p. 116°) (*Wieland* and *Erlenbach*, Ann. **458**, 83). Chinovic acid belongs to the triterpene group since Se dehydro.

genation of pyro-chinovic acid gives 1:8-dimethyl-picene (*Wieland, Hartmann* and *Dietrich*, Ann. **522**, 191; *Ruzicka, Hösli* and *Ehmann*, Helv. **17**, 442). If it has a pentacyclic structure, however, it must contain a double bond and it shows no unsaturated properties. This fact led to the belief that the compound was hexacyclic, but the presence of a double bond is shown by the formation of a bromolactone by the action of Br_2 on pyro-chinovic acid, although acetyl chinovic acid takes up no bromine. The masking of the double bond by a keto group mentioned above (glycyrrhetic acid) is not possible here because the compound is not a ketone; it seems to be masked by the two carboxyl groups, since the dimethyl ester gives a strong colour with $C(NO_2)_4$ like other unsaturated compounds. There is further proof of the presence of a double bond, and hence of a pentacyclic system, in the oxidation of the acetyl dimethyl ester $C_{34}H_{52}O_6$ with CrO_3 to a compound $C_{34}H_{50}O_7$ (*Wieland* and *Hoshino*, Ann. **479**, 201). This product contains one oxygen in place of two hydrogens and shows the characteristic absorption spectrum (maximum at 2500 Å) of an αβ-unsaturated ketone (see glycyrrhetic acid); it can be reduced back to chinovic acid with H_2 and PtO_2, just as glycyrrhetic acid gives a desoxo compound (*Ruzicka* and *Prelog*, Helv. **20**, 1570). *Ruzicka* has suggested the following structure for chinovic acid on analogy with his formula for oleanolic acid.



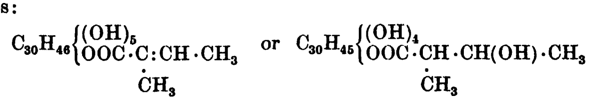
With conc. sulphuric acid chinovic acid undergoes partial lactonisation to the monobasic novic acid $C_{30}H_{44}O_4$, m.p. 255° (methyl ester m.p. 215°) (*Wieland* and *Erlenbach*, Ann. **453**, 83). The oxidation of novic acid and of pyro-chinovic acid has been studied by *Wieland* and his co-workers (Ann. **479**, 179; **488**, 2427; **497**, 140).

Quillaia saponin, $C_{35}H_{56}O_{12}$, m.p. 207°, a dibasic keto-acid (oxime m.p. 258°) isolated from *Quillaia saponaria* (*Hoffmann*, Ber. **36**, 2724; *Stutz*, Ann. **218**, 231; *Hesse*, Ann. **261**, 373), can be hydrolysed to a saturated dihydroxy-keto-carboxylic acid, quillaic acid, $C_{29}H_{46}O_5$, m.p. 294° (diacetate m.p. 250°; oxime m.p. 282°; methyl ester m.p. 225°), and glucuronic acid (*Lehmann*, Z. angew. Chem. **43**, 1118; *Windaus*, Nachr. Ges. Wiss. Göttingen **1925**, 45; *Windaus, Hampe* and *Rabe*, Z. physiol. Chem. **160**, 301).

Benzoin-gum from Siam and Sumatra yields two unsaturated dihydroxy-monocarboxylic acids, **sia-resinolic acid,** $C_{30}H_{48}O_4$, m.p. 240°, $[\alpha]_D + 98{\cdot}5°$ (methyl ester m.p. 181°) and **suma-resinolic acid,** $C_{30}H_{48}O_4$, m.p. 295°, $[\alpha]_D + 102°$ (methyl ester m.p. 220°) (*Winterstein* and *Egli*, Z. physiol. Chem. **202**, 207; *Ruzicka* and *Furter*, Helv. **15**, 472). Sia-resinolic acid is converted by boiling with formic acid into a hydrocarbon $C_{30}H_{44}$, m.p. 188°. Dehydrogenation of the acids gives a dinaphthyl, $C_{25}H_{24}$ (dipicrate m.p. 212°; distyphnate m.p. 226°) together with the naphthalenes and picene obtained from oleanolic acid, etc. The acids thus seem to contain a carbon skeleton similar to that in oleanolic acid (*Ruzicka* and collaborators, Ann. **471**, 25; Helv. **15**, 431; **17**, 442). Suma-resinolic acid is isomeric with hederagenin and resembles oleanolic acid in its behaviour to H_2O_2 and O_3; the first oxidation product is a hydroxy-lactone, $C_{30}H_{48}O_5$, m.p. 322–324°, which is not unsaturated. Hence two hydroxyls must have been added to the double bond, and one of them has formed a lactone with the carboxyl group. The other newly formed hydroxyl group is secondary, since further oxidation gives a ketonic lactone, $C_{30}H_{44}O_5$, m.p. 311–312°, in which one of the original hydroxyl groups and the newly formed one have both been oxidised to keto groups. By analogy with oleanolic acid the double bond is probably in the $\gamma\delta$ position to the carboxyl group, but the $\beta\gamma$ position is not excluded (*Ruzicka, Hösli* and *Hofmann,* Helv. **19**, 109).

Ursolic acid (malol, prunol), $C_{30}H_{48}O_3$, m.p. 285° (acetate m.p. 245°; methyl ester m.p. 222°, see *van der Haar,* Rec. **47** (1928), 585; *Winterstein* and *Stein,* Z. physiol. Chem. **208**, 9), is widely distributed in nature, e.g. in *Arctostaphylos uva ursi,* in the waxy coating of the apple (*van der Haar.* Rec. **48** (1924), 548), in *Prunus serotina* (idem, Rec. **48** (1924), 367, 642), etc. The formation of an isomeric saturated lactone, m.p. 240°, and a bromo-lactone, m.p. 210°, makes the presence of a $\beta\gamma$- or $\gamma\delta$-unsaturated carboxylic acid probable. A secondary alcohol group can be detected by the conversion with chromic acid into the corresponding keto-acid, ursonic acid (methyl ester m.p. 193°; oxime m.p. 244°), and the reduction of the latter by Clemmensen's method to ursanic acid (methyl ester m.p. 118°). Oxidation with $CrO_3 + H_2SO_4$ leads to a diketone, $C_{30}H_{44}O_4$, m.p. 177° (oxime m.p. 211°). When the hydroxyl group is protected by acetylation, the oxidising agent attacks the double bond and gives keto-acetyl-ursolic acid, $C_{32}H_{48}O_5$, m.p. 297° (oxime m.p. 300°; methyl ester m.p. 244°), and keto-acetyl-dehydro-ursolic acid $C_{32}H_{46}O_5$, decomp. 305° (oxime decomp. 335°, methyl ester m.p. 239°; see *Kuwada* and *Matsukawa,* J. Pharm. Soc. Japan **53** (1933), 103). Mild dehydrogenation of benzoyl-ursolic methyl ester, $C_{38}H_{54}O_4$, m.p. 236°, gives dehydro-benzoyl-ursolic methyl ester, $C_{38}H_{52}O_4$, m.p. 212°, and a similar reaction can be carried out with ursanic acid (*Sando,* J. Biol. Chem. **90**, 477). Dehydrogenation: see *van der Haar,* Ber. **55**, 1054; *Ruzicka* and *van Veen,* Z. physiol. Chem. **184**, 69).

Aesculin (escin), $C_{53}H_{88}O_{27}$, m.p. 220–230° (decomp.), the saponin of the horse chestnut, *Aesculus hippocastanum,* was first isolated by *Rochleder* in 1867. Hydrolysis with 5% sulphuric acid at 90° for 40 hours gives aescigenin, $C_{35}H_{58}O_7$, m.p. 311°, $[\alpha]_D + 26{\cdot}8°$ (alc.), together with glucose and glucuronic acid (*van der Haar,* Rec. **42** (1932), 1080; **45** (1926), 271). The aglycone contains one double bond and five free hydroxyl groups; hydrolysis with methyl alcoholic potash eliminates tiglic acid, $C_5H_8O_2$, m.p. 64° (dibromide m.p. 86°, see *Winterstein* and *Blau,* Z. physiol. Chem. **75**, 410; *Winterstein,* ibid. **199**, 25). Hence the compound contains one of the following sets of groups:



$$C_{30}H_{46}\left\{\begin{matrix}(OH)_5\\ OOC\cdot \underset{CH_3}{C}:CH\cdot CH_3\end{matrix}\right. \quad \text{or} \quad C_{30}H_{45}\left\{\begin{matrix}(OH)_4\\ OOC\cdot \underset{CH_3}{CH}\cdot CH(OH)\cdot CH_3\end{matrix}\right.$$

As mentioned in the introduction, dehydrogenation with Se gives sapotalene, $C_{13}H_{14}$ (*Ruzicka* and *van Veen,* Z. physiol. Chem. **184**, 69).

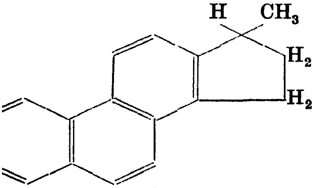
Boswellinic acid, $C_{32}H_{52}O_4$, a violent fish poison from incense (*Olibanum*), has been shown to be a mixture of two isomers, m.p. 255° and 273°, which are hydrolysed to one mol. of acetic acid and one mol. of α-boswellinic acid, $C_{30}H_{50}O_3$, leaflets, m.p. 289°, $[\alpha]_D + 115°$, or of β-boswellinic acid, needles, m.p. 240°, $[\alpha]_D + 118°$ (*Winterstein* and *Stein,* ibid. **208**, 11). When distilled in high vacuum, acetic acid and carbon dioxide are eliminated, giving two hydrocarbons, $C_{29}H_{46}$, m.p. 153°, $[\alpha]_D + 132°$, and $C_{29}H_{48}$, m.p. 141°, $[\alpha]_D + 132°$; these contain non-reactive double bonds (*Beaucourt,* Mo. **53/54**, 897; *Winterstein* and *Stein,* loc. cit.; Ann. **502**, 223). Dehydrogenation: see *Beaucourt,* Mo. **55**, 185.

Camellia saponin, $C_{57}H_{94}O_{30}\cdot 6H_2O(?)$, m.p. 208° (anhyd.), $[\alpha]_D + 37{\cdot}1°$, from *Camellia japonica,* is hydrolysed to its sapogenin, $C_{29}H_{44}O_5(?)$, decomp. 197° (triacetate m.p. 165–175°; oxime decomp. 175–197°), three mol. of glucose and two of arabinose (*Aoyama,* J. Pharm. Soc. Japan **48** (1928), 126).

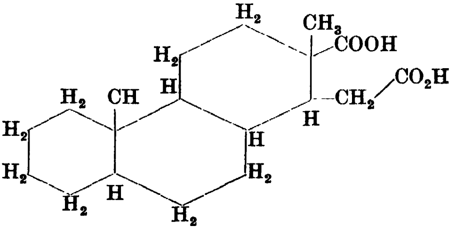
Cyclamin, $C_{63}H_{112}O_{33}$ (or $C_{56}H_{96}O_{29}$) (?), m.p. 254° decomp., $[\alpha]_D - 38{\cdot}6°$ (alc.), from the ordinary cyclamen, *Cyclamen europaeum* (*Plzak*, Ber. **36**,1761; *Kofler*, C. 1927 I 2331; *Bureš* and *Bergauer*, C. 1929 I 2655), is decomposed by dilute mineral acids into cyclamiretin, $C_{35}H_{56}O_5$ (or $C_{28}H_{46}O_4$) (?), m.p. 246°, $[\alpha]_D + 28°$ (diacetate m.p. 214°; oxime m.p. 208°), three mol. of glucose and two of arabinose (*Mutschler*, Ann. **185**, 214; *Dafert*, Arch. Pharm. **264** (1926), 409; *Bureš* and *Bergauer*, C. 1930 I 1798; *Dafert*, C. 1934 I 1785). The sapogenin contains a reactive double bond, since it gives a dibromide. For dehydrogenation, etc. see *Dafert* and *Fettinger*, Arch. Pharm. **268** (1930), 289.

II. The Saponins of the Cholane Group

The saponins of the cholane group, gitonin, digitonin (from *Digitalis purpurea*), and sarsasaponin (parillin) (from *Radix Sarsaparillae*), are hydrolysed to aglycones which, like cholesterol, have an empirical formula with 27 C-atoms. They are derived from the same tetracyclic ring system which is present in the sterols, the bile-acids, the vegetable cardiac aglycones, the toad poisons and the sex hormones. The first careful investigation of this class of compounds was carried out by Kiliani and Windaus. The true nature of the C-skeleton was first revealed, using sarsapogenin (perigenin) and gitogenin, by dehydrogenation with selenium, a process originally applied by Diels to cholesterol (*Diels*, *Gädke* and *Körding*, Ann. **459**, 1). The characteristic dehydrogenation product is the hydrocarbon $C_{18}H_{16}$, 3-methyl-cyclopenteno-phenanthrene, Diels' hydrocarbon (I; see also p. 553) (*Jacobs* and *Simpson*, Am. **56**, 1424; J. Biol. Chem. **105** (1934), 501).



(I)



(II)

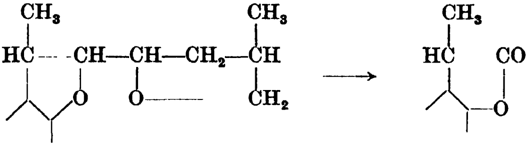
These results were fully confirmed by the oxidative degradation of the side-chain of tigonin, which was discovered later. From the genin of this

Saponin	Formula	M.P.	$[\alpha]_D$	Sapogenin
Tigonin	$C_{56}H_{92}O_{27}$	—	—	Tigogenin
Gitonin	$C_{50}H_{82}O_{23}$	272°	—50·7°	Gitogenin
Digitonin	$C_{56}H_{92}O_{29}$	235°	—54·3°	Digitogenin
Sarsaponin (Parillin)	$C_{45}H_{76}O_{17}$	240°	—66°	Sarsapogenin, (Parigenin)

saponin *Tschesche* and *Hagedorn* (Ber. **68**, 1412) obtained aetio-allo-bilianic acid, $C_{19}H_{30}O_4$ (II), a stereoisomer of the dicarboxylic acid obtained by successive degradation of the side-chain of cholanic acid (see p. 556).

These investigation, and the fact that the molecule contains 27 C-atoms, show that these sapogenins are derived from the tetracyclic ring-system of the sterols (19 C-atoms), with a side-chain of eight C-atoms, which is probably similar to that of cholesterol (pp. 548, 554). Since digitonin (p. 523) can be shown by simple reactions to be related to gitonin and tigonin, the same holds for this saponin (*Tschesche*, Ber. **68**, 1090).

The side-chain of all neutral saponins of the cholane type contains two indifferent ethereal oxygen atoms. In the dehydrogenation it is usually isolated as methyl-isohexyl ketone (*Ruzicka* and *van Veen*, Z. physiol. Chem. **184**, 69; *Jacobs* and *Simpson*, loc. cit.), or sometimes as an unsaturated hydroxy-ketone, $C_8H_{14}O_3$ (semicarbazone m.p. 120°). Oxidation of digitogenic acid yields part of the side-chain as α-methyl-glutaric acid (*Windaus* and *Willerding*, Z. physiol. Chem. **143**, 45). The behaviour of the side-chain of the the sapogenins on vigorous oxidation with fuming nitric acid is characteristic; five C-atoms are lost with the formation of a lactone with 22 C-atoms. This important reaction was first shown with gitogenic acid (*Windaus* and *Linsert*, ibid. **147**, 275), and later with ditogenic acid (*Windaus* and *Shah*, ibid. **151**, 86):



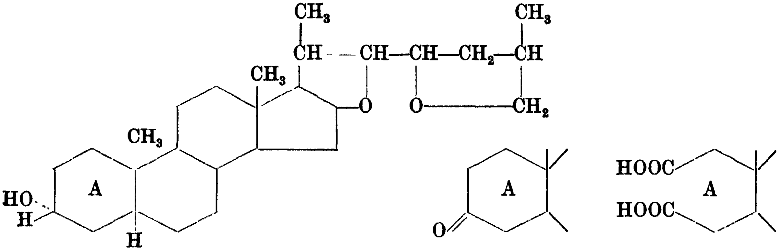
The table below summarises the more important saponins and their aglycones.

Literature: — *Fieser*, The Chemistry of the Natural Products related to Phenanthrene, New York, 1936; *Inhoffen* and *Lettré*, Über Sterine, Gallensäuren und verwandte Naturstoffe, Stuttgart, 1936; *Waese*, Digitalis, Leipzig, 1936; *Tschesche*, Erg. Physiol. biol. Chem. exp. Pharmakol. **38** (1936), 31–72.

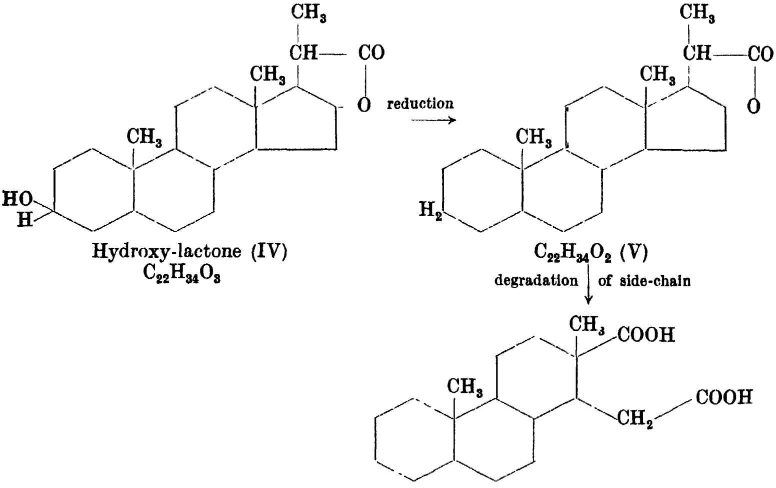
Tigogenin: $C_{27}H_{44}O_3$ (I), m.p. 204°, $[\alpha]^{25}_{D}$ — 49° (pyridine), $[\alpha]^{18}_{D}$ — 67·2° ($CHCl_3$); acetyl compound m.p. 202°, $[\alpha]_D$ — 57° (pyridine); this has been isolated only comparatively recently from *Digitalis purpurea* (*Jacobs* and *Fleck*, J. Biol. Chem. **88** (1935), 545), and from *Digitalis lanata* (*Tschesche*, Ber. **68**, 1090). It contains a secondary alcohol group, and by mild oxidation with CrO_3 it gives the corresponding ketone, tigogenone (II), $C_{27}H_{42}O_3$, m.p. 207°, $[\alpha]_D$ — 35° (pyridine), oxime m.p. 256 decomp., while energetic oxidation yields gitogenic acid (III), m.p. 242° (*Tschesche*, Ber. **68**, 1091). The Clemmensen reduction of tigogenone gives $C_{27}H_{44}O_2$, m.p. 265–267°.

Formula	M.P.	$[\alpha]_D$	M.P. Acetyl Compd.	Sugar
$C_{27}H_{44}O_3$	204°	—49° (pyr.)	202°	2 mol. glucose; 2 mol. galactose; 1 mol. xylose
$C_{27}H_{44}O_4$	272°	—66·5°	244°	3 mol. galactose; 1 mol. pentose
$C_{27}H_{44}O_5$	280°	—81·0° ($CHCl_3$)	190°	2 mol. glucose; 2 mol. galactose; 1 mol. xylose
$C_{27}H_{44}O_3$	200°	—67·6°	130°	2 mol. glucose; 1 mol. rhamnose

Tigogenin forms with digitonin a molecular compound difficultly soluble in alcohol. Energetic oxidation of the acetyl compound of tigogenin with CrO_3 removes five C-atoms of the side-chain to form the acetate of a hydroxy-lactone, $C_{22}H_{34}O_3$ (IV), m.p. 233·5°, $[\alpha]_D - 41{\cdot}2°$ (CHCl), which can be converted, via the ketolactone $C_{22}H_{32}O_3$, m.p. 254°, $[\alpha]_D^{18} - 22{\cdot}8°$ ($CHCl_3$), into the fundamental hydroxyl-free lactone $C_{22}H_{34}O_2$ (V). Further degradation of the side-chain of this lactone led to aetio-allo-bilianic acid, $C_{19}H_{30}O_4$ (m.p. 253° decomp.) (*Tschesche*, Ber. **68**, 1412), which proved for the first time the presence of the sterol skeleton in tigogenin. These degradations are explained in the following formulae:



Tigogenin (I) Tigogenone (II) Gitogenic acid (III)

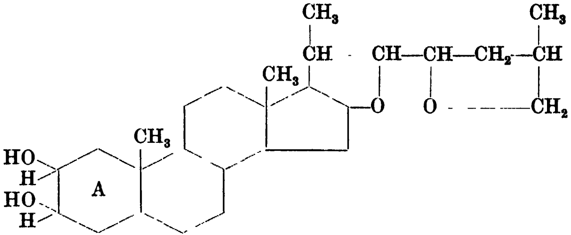


Hydroxy-lactone (IV) $C_{22}H_{34}O_3$

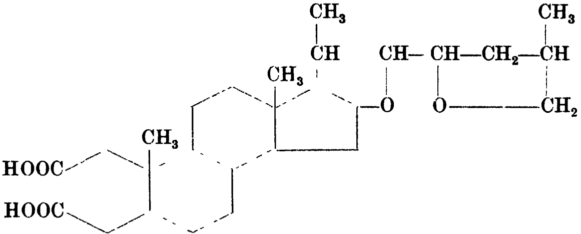
$C_{22}H_{34}O_2$ (V)

Aetio-allo-bilianic acid

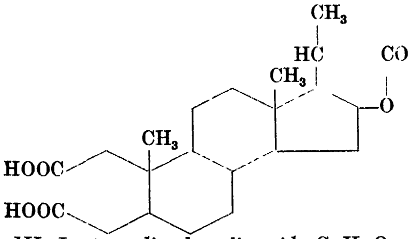
Gitonin, $C_{50}H_{82}O_{23}$, m.p. 272° decomp., $[\alpha]_D - 50{\cdot}7°$ (pyridine), which normally accompanies digitonin (see below), was first obtained crystalline by *Windaus* and *Schneckenburger* (Ber. **46**, 2628), and soon after by *Kiliani* (Ber. **49**, 701). Its preparation in the pure state is extremely tedious. Acid hydrolysis yields **gitogenin,** $C_{27}H_{44}O_4$, m.p. 272°, $[\alpha]_D - 66{\cdot}5°$ (desoxy-digitogenin), together with three mol. of galactose and one of a pentose; its diacetyl compound has m.p. 243–244°. Gitogenin (I) contains two secondary hydroxyl groups, which are adjacent to one another in the same 6-ring; this ring is opened on oxidation with the formation of a dicarboxylic acid, gitogenic acid, $C_{27}H_{42}O_6$, m.p. 242–243° (II), dimethyl ester m.p. 145° (*Windaus* and *Schneckenburger*, loc. cit.). Energetic oxidation with fuming nitric acid opens the ring and eliminates five C-atoms from the side-chain, forming a lactone-dicarboxylic acid, $C_{22}H_{32}O_6$, m.p. 238° (III); dimethyl ester m.p. 156° (*Windaus* and *Linsert*, Z. physiol. Chem. **147**, 275). When heated with acetic anhydride, the lactone-dicarboxylic acid eliminates CO and H_2O, yielding the pentacyclic ketone, $C_{21}H_{30}O_3$, m.p. 226° (oxime m.p. 250° decomp.) (IV); this proves that gitogenic acid and the lactone-dicarboxylic acid obtained from it are formed by the opening of the 6-ring A. Gitogenic acid can also be obtained from digitogenic acid (keto-gitogenic acid), $C_{27}H_{40}O_7$ (p. 524), by reducing of one of the keto-groups of the latter by the Wolff-Kishner method; this is a simple reaction which shows the connection between gitogenin and digitogenin. Dehydrogenation of gitogenin with Se (*Jacobs* and *Simpson*, Am. **56**, 1424) gives a simple ketone, $C_8H_{16}O$ (semicarbazone m.p. 144–145°), and Diels' hydrocarbon, $C_{18}H_{16}$, m.p. 123·5–124° (3-methyl-cyclopentenophenanthrene):



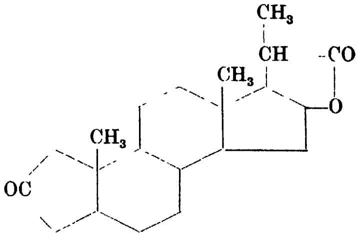
I. Gitogenin: $C_{27}H_{44}O_4$



II. Gitogenic acid: $C_{27}H_{42}O_6$



III. Lactone-dicarboxylic acid: $C_{22}H_{32}O_6$



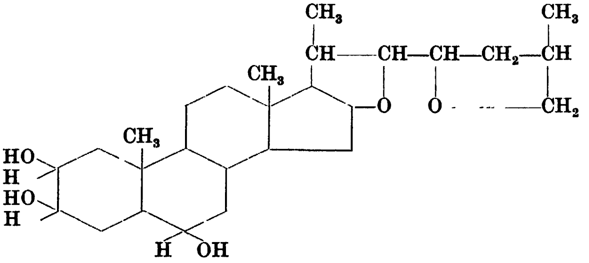
IV. Pyro-ketone: $C_{21}H_{30}O_3$

The *Digitalis* saponin upon which most work has been done is **digitonin**, $C_{56}H_{92}O_{29}$, m.p. 235°, $[\alpha]_D$ — 54·3° (75% acetic acid). This glycoside has been investigated chiefly by *Kiliani* (coll. lit. Ber. **51** 1613), and later (from 1922) by *Windaus* and his collaborators (Z. physiol. Chem. **121**, 63; **132**, 33; **151**, 86).

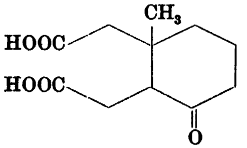
A characteristic property of digitonin is the formation of molecular compounds with most sterols, several bile-acids and cardiac poisons (below) or their genins, which are sparingly soluble in 90% alcohol. A free hydroxyl group on C_3 of the cholane nucleus and the cis-position of this hydroxyl to the methyl group on C_{10} is necessary for this reaction[1] (*Windaus*, Ber. **42**, 238; *Fernholz*, Z. physiol. Chem. **232**, 97).

Digitonin can be separated from the gitonin which accompanies it only with considerable difficulty; it is hydrolysed by alcoholic HCl to two mol. of *d*-glucose, two of galactose, one of xylose (*Kiliani*, Ber. **59**, 2462) and **digitogenin** (I) (hydroxy-gitogenin), $C_{27}H_{44}O_5$, m.p. 280°, $[\alpha]_D - 81{\cdot}0^0$ ($CHCl_3$). Acetylation shows that digitogenin contains three secondary hydroxyl groups (triacetyl compound m.p. 190°), while the other two O-atoms are present in the side-chain as ether links. Oxidation with CrO_3 yields digitogenic acid (keto-gitogenic acid), $C_{27}H_{40}O_7$ (II), m.p. 210° (dimethyl ester m.p. 146°), which is converted by boiling alkali into the stereoisomeric digitoic acid, m.p. 240° (dimethyl ester m.p. 140°), and by reduction of the keto-group by the Kishner-Wolff method into gitogenic acid, $C_{27}H_{40}O_6$ (see above) (*Tschesche*, Ber. **68**, 1090). Digitogenin, tigogenin (p.521) and gitogenin can therefore be converted into the same dicarboxylic acid. Further oxidation of digitogenic or digitoic acids with $KMnO_4$ leads to oxy-digitogenic acid (III), $C_{27}H_{40}O_9$, m.p. 275° (trimethyl ester m.p. 153°), a keto-tricarboxylic acid, shown to be a β-ketonic acid by the ease with which it loses CO_2 on heating (*Kiliani*, Ber. **24**, 344; *Windaus* and *Weil*, Z. physiol. Chem. **121**, 73). More vigorous oxidation of oxy-digitogenic acid with permanganate and conc. alkali gives digitoic acid, $C_{27}H_{40}O_{10}$, m.p. 192° (trimethyl ester m.p. 138°), a hydroxy-keto-tricarboxylic acid (*Kiliani*, Ber. **24**, 346; **37**, 1216; 43, 3565; *Windaus* and *Weil*, loc. cit.). Other compounds are obtained when digitogenic acid is oxidised further with CrO_3 (*Kiliani*, Ber. **49**, 702; *Windaus* and *Willerding*, Z. physiol. Chem. **143**, 37); a pentacarboxylic acid, $C_{27}H_{40}O_{12}$, m.p. 223° (probably IV), and its decarboxylation product, the tetracarboxylic acid (V), $C_{26}H_{40}O_{10}$, m.p. 267° (tetramethyl ester m.p. 125°). These polycarboxylic acids contain a newly formed carboxyl group in the side-chain, and at the same time part of the side-chain is split off and isolated as α-methyl-glutaric acid, m.p. 76° (dianilide m.p. 175° (*Windaus* and *Willerding*, loc. cit., p. 45).

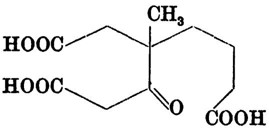
It is important to note that digitoic acid (see above) is oxidised by nitric acid with the loss of five C-atoms of the side-chain to give derivatives of an acid with 22 C-atoms, and hence behaves like gitogenic acid (*Windaus* and *Shah*, Z. physiol. Chem. **151**, 87).



I. Digitogenin: $C_{27}H_{44}O_5$



II. Digitogenic acid: $C_{27}H_{40}O_7$



III. Oxy-digitogenic acid: $C_{27}H_{40}O_9$

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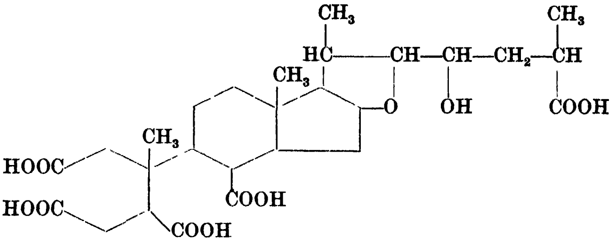
[1] For the numbering of the cholane system see p. 529.



IV. Pentacarboxylic acid: $C_{27}H_{40}O_{12}$.

Sarsasaponin (parillin), $C_{45}H_{76}O_{17}$, m.p. 240°, $[\alpha]_D$ — 66°, is prepared from *Radix sarsaparillae* from Honduras and Vera Cruz (*Kaufmann* and *Fuchs*, Ber. **56**, 2527; *van der Haar*, Rec. **48** (1930), 726.) Hydrolysis gives two mol. of glucose, one of rhamnose and **sarsasapogenin** (parigenin), $C_{27}H_{44}O_3$, m.p. 200°, $[\alpha]_D$ — 67·6° (acetyl deriv., m.p. 130°). Oxidation converts the secondary alcohol group into a ketonic group, giving sarsasapogenone, $C_{27}H_{42}O_3$, m.p. 223°, $[\alpha]_D$ — 46° (pyridine); oxime m.p. 127°; further oxidation yields the dicarboxylic acid, $C_{27}H_{42}O_6$, m.p. 280° decomp. With nitric acid, this dicarboxylic acid behaves like gitogenic acid (p. 523); five C-atoms are eliminated from the side-chain to give a lactone-dicarboxylic acid $C_{22}H_{36}O_6$, m.p. 295°, dimethyl ester m.p. 172° (*Simpson* and *Jacobs*, J. Biol. Chem. **109** (1935), 573). Methyl-isohexyl-ketone is isolated in the dehydrogenation (*Ruzicka* and *van Veen*, Z. physiol. Chem. **184** (1929), 69). In later experiments on the dehydrogenation with Se (*Jacobs* and *Simpson*, J. Biol. Chem. **105** (1934), 501) the hydrocarbon $C_{18}H_{16}$, 3-methyl-cyclopentenophenanthrene, was obtained, showing that this sapogenin has the cholane skeleton. Sarsasapogenin is isomeric with tigogenin and also contains a hydroxyl group at C_3, as is indicated by the properties of its surface films (*Askew*, *Farmer* and *Kon*, J. **1936**, 1399). *Tschesche*'s method of relating these compounds to the bile acids (p. 549) has been applied to this sapogenin (*Farmer* and *Kon*, J. **1937**, 414), and the product is aetio-bilianic acid, and not the allo-acid obtained from tigogenin. Hence it belongs to the coprostane series and must be a stereoisomer of tigogenin, from which it differs in the configuration at C_5 (see formula of tigogenin, p. 522).

Jamaica sarsaparilla also contains a saponin which on hydrolysis gives a sapogenin, **smilagenin** $C_{27}H_{44}O_3$, m.p. 183–184°, $[\alpha]_D^{25} = -69°$ ($c = 0.311$ in $CHCl_3$), $[\alpha]_D^{25} = -61°$ ($c = 0.339$ in MeOH) (*Askew*, *Farmer* and *Kon*, J. **1936** 1399). This is isomeric with sarsasapogenin and its acetyl derivative loses most of its side chain on oxidation with CrO_3 to give an acetyl lactone identical with that obtained from sarsasapogenin. Hence the difference between the two compounds lies solely in the last five C atoms of the side chain, and probably consists in a difference in configuration about the asymmetric C atom which they contain (see formula of tigogenin, p. 522) (*Farmer* and *Kon*, J. **1937**, 414).

f) THE CARDIAC POISONS OF THE CHOLANE GROUP[1]

The cardiac poisons which will now be discussed are related in constitution to the saponins digitonin, gitonin and sarsasaponin. In therapeutic doses these compounds have a stimulating action on the heart, but in greater quantities they behave as violent poisons; they therefore play an important part in the therapy of heart diseases (cf. *Edens*, Klin. Woch. **1935**, 809).

These compounds are, for the most part, glycosides which can be hydrolysed more or less readily by the usual methods (mineral acids, enzymes) to the aglycone and the sugar components (*d*-glucose, *l*-rhamnose $C_6H_{12}O_5$, digitoxose[1] = deoxy-methyl-pentose $C_6H_{12}O_4$, cymarose[2] = 3-methyl ether of digitoxose, and digitalose[3] = 2-methyl ether of an aldomethyl pentose, $C_7H_{14}O_5$). The aglycones contain 23 or 24 C-atoms, and as with the above saponins, it has been shown that the cardiac aglycones also possess the tetracyclic skeleton of the sterols and bile-acids, and thus the relationship which had often been postulated between these classes of substances has found experimental confirmation (*Windaus* and *Hermanns*, Ber. **48**, 991; *Windaus* and *Bandte*, Ber. **56**, 2002).

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[1] *W. A. Jacobs*, The Chemistry of the Cardiac Glucosides, Physiol. Rev. **13** (1933), 221; *R. C. Elderfield*, The Chemistry of the Cardiac Glycosides, Chem. Rev. **17** (1935), 187.

The main points of the evidence are as follows:

1. Dehydrogenation of anhydro-uzarigenin (*Tschesche*, Z. physiol. Chem. **222**, 58), of strophanthidin (*Jacobs* and *Elderfield*, Science **79** (1933), 279) and of cinobufagin (*Tschesche* and *Offe*, Ber. **68**, 1998) with Se yields 3-methyl-cyclopentenophenanthrene (Diels' hydrocarbon).
2. Successive oxidative degradation of the lactonic side-chain attached to the tetracyclic skeleton converts both uzarigenin (*Tschesche*, Z. physiol. Chem. **229**, 219; Ber. **68**, 7) and digitoxigenin (*Jacobs* and *Elderfield*, Science **80** (1934), 434; J. Biol. Chem. **108** (1934), 497) into the aetiocholanic acids, $C_{20}H_{32}O_2$.
3. Anhydro-scillaridin with 24 C-atoms can be converted by an unambiguous series of reactions into allo-cholanic acid, $C_{24}H_{40}O_2$ (*Stoll*, Helv. **18**, 647).

I. Vegetable Cardiac Poisons with an Aglycone of 23 C-atoms

Cardiac glycosides of this type are found chiefly in the following families of plants: *Scrophulariaceae*, *Apocynaceae*, *Asclepiadaceae*, *Moraceae* and *Liliaceae*. The following table summarises the most important compounds, their aglycones and sugar components:

Glycoside	Formula	M.P.	$[\alpha]_D$	Aglycone	Formula
Digitalin	$C_{36}H_{56}O_{14}$	229°	+ 14·2°	digitaligenin[4]	$C_{23}H_{30}O_3$
Oleandrin	$C_{30}H_{46}O_8$	249°	—	digitaligenin[4]	$C_{23}H_{30}O_3$
Digitoxin	$C_{41}H_{64}O_{13}$	263°	+ 32·6°	digitoxigenin	$C_{23}H_{34}O_4$
Thevetin	$C_{42}H_{66}O_{18}$	195°	—	thevetigenin[5]	$C_{23}H_{34}O_4$
Uzarin	$C_{35}H_{54}O_{14}$	270°	— 27°	uzarigenin[5]	$C_{23}H_{34}O_4$
Gitoxin	$C_{41}H_{64}O_{14}$	285°	+ 3·5°	gitoxigenin	$C_{23}H_{34}O_5$
Gitalin	$C_{35}H_{56}O_{12}$	155°	— 25·2°	gitoxigenin	$C_{23}H_{34}O_5$
Digoxin	$C_{41}H_{64}O_{14}$	265°	+ 13·3°	digoxigenin	$C_{23}H_{34}O_5$
Sarmentocymarin	$C_{30}H_{46}O_8$	—	— 12·2°	sarmentogenin	$C_{23}H_{34}O_5$
Periplocin	$C_{36}H_{56}O_{13}$	—	—	periplogenin	$C_{23}H_{34}O_5$
k-Strophanthin	$C_{36}H_{54}O_{14}$	178°	+ 10°	k-strophanthidin	$C_{23}H_{32}O_6$
Cymarin	$C_{30}H_{44}O_9$	138°	+ 23·3°	k-strophanthidin	$C_{23}H_{32}O_6$
Convallatoxin ..	$C_{29}H_{42}O_{10}$	239°	0°	convallatoxigenin	$C_{23}H_{32}O_6$
α-Antiarin	$C_{29}H_{42}O_{11}$	—	—	antiarigenin[5]	$C_{23}H_{32}O_7$
β-Antiarin	$C_{29}H_{42}O_{11}$	—	—	antiarigenin[5]	$C_{23}H_{32}O_7$
Ouabain .. .. (g-Strophanthin)	$C_{29}H_{44}O_{12}$	188°	— 30°	ouabagenin (g-strophanthidin)	$C_{23}H_{34}O_8$

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[1] *Kiliani*, Ber. **38**, 4040; **55**, 88, 1515, 2503; *Micheel*, Ber. **63**, 347; *Windaus* and *Schwarte*, C. 1927 I 882; 1930 I 2237.

[2] *Kiliani*, Ber. **48**. 979; *Bergmann*, *Schotte* and *Leschinsky*, Ber. **56**, 1052; *Elderfield*, J. biol. Chem. **111** (1935), 527.

[3] *Kiliani*, Ber. **49**, 709; **55**, 90; **63**, 2866; **64**, 2027; *Schmidt* and *Zeiser*, [Ber. **67**, 2129

[4] Dianhydro-gitoxigenin.

[5] Isolated only as anhydro- or dianhydro-compounds.

Digitoxin, gitoxin and digoxin were for some time considered to be the actual glycosides present in the plants. The work of Stoll and his collaborators, however, has established beyond any doubt that glycosides richer in sugars are present in the plant material, and that the substances given in the table represent hydrolysis products of the actual glycosides, formed by the action of enzymes (Helv. **16**, 1052). Under conditions that avoid enzymatic hydrolysis, Stoll and Kreis isolated the true glycosides from *Digitalis lanata* and from *Digitalis purpurea*, and showed that they were both richer by one glucose residue, while the *lanata* glycoside contained also an acetic acid residue.

The following glycosides have been isolated in a crystalline condition from *Digitalis purpurea* (*Stoll* and *Kreis*, Helv. **18**, 120):

purpurea glycoside A, $C_{47}H_{74}O_{18}$, m.p. 240° (decomp.), $[\alpha]_D + 12{\cdot}1^\circ$ (75% alc.).
purpurea glycoside B, $C_{47}H_{74}O_{19}$, m.p. 238–240° (decomp.), $[\alpha]_D + 20{\cdot}4^\circ$.

From *Digitalis lanata* they obtained (Helv. **16**, 1052):

digilanide A, $C_{49}H_{76}O_{19}\cdot H_2O$, m.p. 245–248°, $[\alpha]_D + 31{\cdot}1^\circ$
digilanide B, $C_{49}H_{76}O_{20}$, m.p. 245–248°, $[\alpha]_D + 36{\cdot}7^\circ$
digilanide C, $C_{49}H_{76}O_{20}$, m.p. 245–248°, $[\alpha]_D + 33{\cdot}4^\circ$.

The complete acid hydrolysis of these glycosides gives:

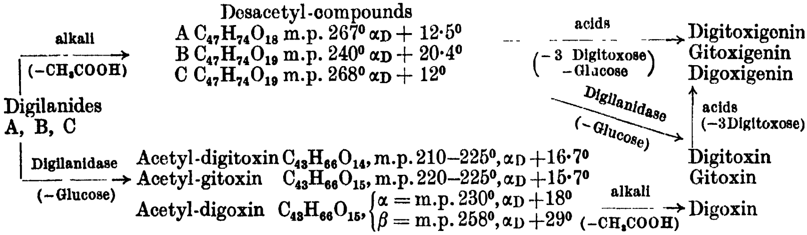
$$\left.\begin{array}{l} C_{47}H_{74}O_{18} + 4H_2O = \underset{\text{digitoxigenin}}{C_{23}H_{34}O_4} \\ C_{47}H_{74}O_{19} + 4\,H_2O = \underset{\text{gitoxigenin}}{C_{23}H_{34}O_5} \end{array}\right\} + \underset{\text{3 digitoxose}}{3\,C_6H_{12}O_4} + \underset{\text{glucose}}{C_6H_{12}O_6}$$

M.P.		Sugar	Occurrence
213°	+ 56·9°	digitalose, glucose	*Digitalinum verum*
213°	+ 56·9°	cymarose	*Nerium oleander*
250°	+ 19·1°	3 digitoxose	*Digitalis purpurea*, *Digitalis lanata*
—	—	2 glucose, 1 methyl-ether hexose	*Thevetia neriifolia*
—	—	2 glucose	*Gomphocarpus* species
235°	+ 32·6°	3 digitoxose	*Digitalis purpurea*, *Digitalis lanata*
235°	+ 32·6°	2 digitoxose	*Digitalis purpurea*
222°	+ 27°	3 digitoxose	*Digitalis lanata*
270°	+ 21·3°	sarmentose	*Strophanthus sarmentosus*
185°	+ 31·5°	glucose, cymarose	*Periploca graeca*
175°	+ 43°	glucose, cymarose	*Strophanthus kombé*
175°	+ 43°	cymarose	*Strophanthus kombé*
—	—	rhamnose	*Convallaria majalis*
—	—	antiarose	*Antiaris toxicaria*
—	—	rhamnose	*Antiaris toxicaria*
175°	—	rhamnose	*Strophanthus gratus*; bark of the ouaba-tree

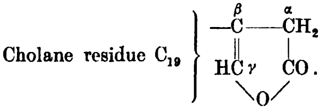
$$\left.\begin{array}{l} C_{49}H_{76}O_{19} + 5\,H_2O = \underset{\text{digitoxigenin}}{C_{23}H_{34}O_4} \\ C_{49}H_{76}O_{20} + 5\,H_2O = \underset{\text{gitoxigenin}}{C_{23}H_{34}O_5} \\ C_{49}H_{76}O_{20} + 5\,H_2O = \underset{\text{digoxigenin}}{C_{23}H_{34}O_5} \end{array}\right\} + \underset{\text{3 digitoxose}}{3\,C_6H_{12}O_4} + \underset{\text{glucose}}{C_6H_{12}O_6} + \underset{\text{acetic acid}}{C_2H_4O_2}$$

The acetylated *lanata* glycosides can be converted by mild hydrolysis with alkali into the purpurea glycosides. Purpurea glycoside A is identical with desacetyl-digilanide A (*Stoll* and *Kreis*, Helv. **18**, 120).

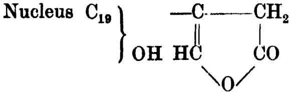
Partial enzymatic hydrolysis of the true glycosides gives the glycosides, digitoxin, gitoxin and digoxin, which are shown in the table. The following possible stages in the hydrolysis have been realised (*Stoll*, Helv. **16**, 1390; **17**, 592; **18**, 120):


Desacetyl-compounds
A $C_{47}H_{74}O_{18}$ m.p. 267° αD + 12·5°
B $C_{47}H_{74}O_{19}$ m.p. 240° αD + 20·4°
C $C_{47}H_{74}O_{19}$ m.p. 268° αD + 12°
alkali
(−CH_3COOH)
Digilanides A, B, C
Digilanidase
(−Glucose)
acids
(−3 Digitoxose −Glucose)
Digitoxigenin
Gitoxigenin
Digoxigenin
Digilanidase
(−Glucose)
acids
(−3Digitoxose)
Acetyl-digitoxin $C_{43}H_{66}O_{14}$, m.p. 210–225°, αD +16·7°
Acetyl-gitoxin $C_{43}H_{66}O_{15}$, m.p. 220–225°, αD +15·7°
Acetyl-digoxin $C_{43}H_{66}O_{15}$, α = m.p. 230°, αD +18°; β = m.p. 258°, αD +29°
alkali
(−CH_3COOH)
Digitoxin
Gitoxin
Digoxin

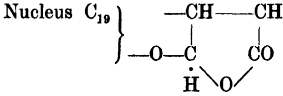
The empirical formulae show that the various aglycones differ essentially by an increasing content of oxygen. All the aglycones (genins) are unsaturated lactones of an enolised γ-aldehydo-acid, the β-carbon atom of which is combined with the tetracyclic nucleus.



Several reactions which are common to all aglycones of this series are due to the presence of this grouping. The lactone ring is opened in all cases by warming with alcoholic alkali. A very important fact is that acidification gives neither the free aldehydo-acid nor the original aglycone, but invariably leads to an **iso-compound,** which is of a lactonic nature, but saturated. We owe this knowledge of the structure of the lactonic group and of this isomerisation, which is common to all the aglycones, to the work of Jacobs[1] and his collaborators. According to their results, a hydroxyl group attached to the cyclic nucleus and in the δ-position to the aldehyde group takes part in the isomeric change.



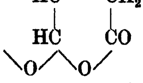
aglycone



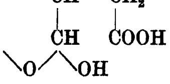
iso-aglycone

Two stereoisomeric iso-compounds are often formed, a fact which seems very reasonable because two new centres of asymmetry are formed.

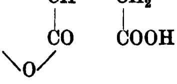
The iso-compounds are also lactones, and are hydrolysed by warm alkali to lactol-carboxylic acids; the latter are oxidised by hypochlorite to lactone-carboxylic acids, the **iso-acids:**



iso-compound



lactol-carboxylic acid
(in equil. with hydroxy-
aldehyde-carboxylic acid)



iso-acid

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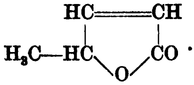
[1] *Jacobs* and *Collins*, J. Biol. Chem. **64** (1925), 383; **65**, 491.

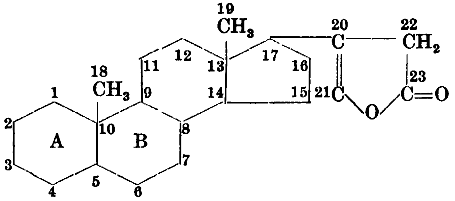
A colour reaction common to all the genins is due to the presence of this βγ-unsaturated lactone group; this is the Legal test: the genins dissolved in pyridine give a red colour with nitroprusside and alkali. It is important to note that the Legal test is also positive with βγ-angelica-lactone,



. Dihydro-aglycones and iso-aglycones which contain a saturated lactone group do not give the colour.

The aglycones given in the table above differ chiefly in an increasing number of oxygen atoms; these are present as hydroxyl groups, and to some extent also as an aldehyde group (k-strophanthidin, antiarigenin) or as a primary alcohol group (ouabagenin). This is the reason why many aglycones can be converted by removal of the nuclear hydroxyls into one and the same saturated fundamental lactone, $C_{23}H_{36}O_2$, which was first obtained by Windaus and Stein from digitoxigenin (Ber. 61, 2436) (cf. the various genins).

The various genins are thus substitution products of the following unsaturated lactone:



The following table summarises the positions, so far as they are established, of the substituents in the cyclic nucleus in the genins.

Aglycone	Formula	Positions of OH groups	Other substituents	Double bonds
Uzarigenin	$C_{23}H_{34}O_4$	C_3, C_{14}	CH_3 on C_{10}	1
Thevetigenin.	$C_{23}H_{34}O_4$	C_3, C_{14}	CH_3 on C_{10}	1
Digitoxigenin	$C_{23}H_{34}O_4$	C_3, C_{14}	CH_3 on C_{10}	1
Digoxigenin	$C_{23}H_{34}O_5$	C_3, C_{14}, C_{11}	CH_3 on C_{10}	1
Sarmentogenin	$C_{23}H_{34}O_5$	C_3, C_{14}, C_{11}	CH_3 on C_{10}	1
Gitoxigenin	$C_{23}H_{34}O_5$	C_3, C_{14}, C_{16}	CH_3 on C_{10}	1
(Digitaligenin	$C_{23}H_{30}O_3$	C_3	CH_3 on C_{10}	3)
Periplogenin	$C_{23}H_{34}O_5$	C_3, C_{14}, C_5	CH_3 on C_{10}	1
k-Strophanthidin	$C_{23}H_{32}O_6$	C_3, C_{14}, C_5	CHO on C_{10}	1
Convallatoxigenin	$C_{23}H_{32}O_6$	C_3, C_{14}, ?	CH_3 on C_{10}	2
Antiarigenin	$C_{23}H_{32}O_7$	? ? ? ?	CHO on C_{10}	2
Ouabagenin (g-Strophanthidin) } . .	$C_{23}H_{34}O_8$	C_3, C_{14}, ? ?	CH_2OH on C_{10}	1

The sugar residues are probably attached to the OH on C_3.

As regards the spatial configuration of the skeleton, most aglycones have rings A and B joined in the cis-decalin configuration. An exception is uzarigenin, in which the rings are in the trans configuration. In several genins the spatial configuration of rings A and B has not yet been determined; the aetiocholanic acids formed by degradation of the lactonic side-chain are of great importance for determining this spatial configuration.

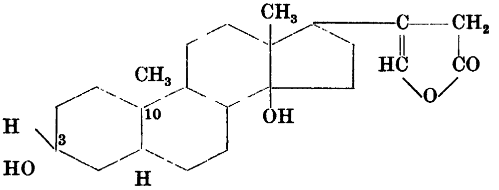
Genins in which the OH group on C_3 is on the same side of the ring A (cis-) as the methyl group on C_{10} give molecular compounds with digitonin which are almost insoluble in 90% alcohol; this is in agreement with the results in the sterol and bile acid series. Examples of such compounds are uzarigenin and thevetigenin.

Most of the genins are related to one another by unambiguous reactions. Thus k-strophanthidin can be converted, via its iso-compound, into iso-periplogenic acid, and this again can give a derivative of iso-digitoxigonic acid (see p. 538). In the same way, gitoxigenin and digitoxigenin, digoxigenin and digitoxigenin, and thevetigenin and digitoxigenin can be converted into identical derivatives.

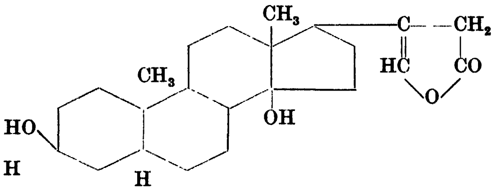
Several aglycones are stereoisomers; uzarigenin is stereoisomeric with thevetigenin, and digitoxigenin and digoxigenin are stereoisomeric with sarmentogenin. Further details will be found under the various aglycones.

Thevetigenin, Digitoxigenin and Uzarigenin, $C_{23}H_{34}O_4$

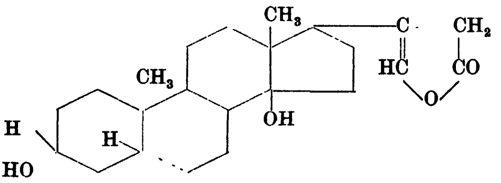
Thevetigenin, the aglycone of thevetin, is stereoisomeric with digitoxigenin from the glycoside digitoxin; this isomerism depends upon the spatial configuration of the OH group on C_3. If the asymmetry is removed by oxidation of anhydro-thevetigenin or of tetrahydro-anhydro-thevetigenin with CrO_3, the product is anhydro-digitoxigenone or its tetrahydro-derivative. The fact that anhydro-thevetigenin gives a slightly soluble molecular compound with digitonin, in contrast to digitoxigenin, indicates that the OH on C_3 and the CH_3 on C_{10} are in the cis position, while in digitoxigenin they are in the trans position (*Jacobs* and *Elderfield,* Science **80** (1934), 434; J. Biol. Chem. **108** (1934), 497):



Thevetigenin



Digitoxigenin



Uzarigenin

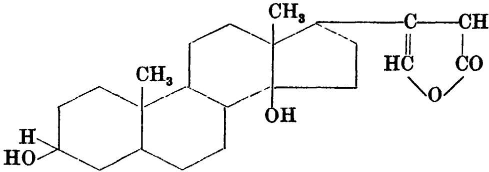
Jacobs and *Elderfield* (loc. cit.) degraded tetrahydro-anhydro-digitoxigenin to aetiocholanic acid; a similar degradation carried out upon uzarigenin by *Tschesche* (Z. physiol. Chem. **229**, 219; Ber. **68**, 7) yielded the stereoisomeric aetio-allo-cholanic acid. This proves that the two genins are stereoisomers which differ in configuration at the union of rings A and B.

Thevetin, $C_{42}H_{66}O_{18}$, m.p. 195° decomp., was first isolated from the yellow oleander (*Thevetia neriifolia*) (*Chen* and *Chen*, J. Biol. Chem. **105** (1934), 231).

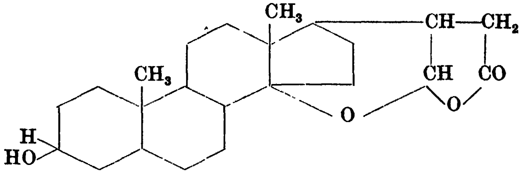
Iso-thevetin, m.p. 238°, is obtained from thevetin by boiling for $^3/_4$ hour with N/10 methyl alcoholic alkali, followed by acidification. Hydrolysis with HCl gives two mol. of glucose, which is present in the glycoside as gentiobiose, one of the methyl ether of a hexose, and **thevetigenin** $C_{23}H_{34}O_4$, a non-crystalline isomer of digitoxigenin and of uzarigenin.

Anhydro-thevetigenin, $C_{23}H_{32}O_3$, m.p. 220, $[\alpha]_D^{18}$ + 40·0° ($CHCl_3$), is formed by energetic acid hydrolysis. It forms a difficultly soluble compound with a 1% solution of digitonin. The ketone obtained by careful oxidation of anhydro-thevetigenin with CrO_3 is identical with anhydro-digitoxigenone, m.p. 270° (*Windaus* and *Stein*, Ber. **61**, 2436; *Tschesche*, Ber. **69**, 2372). In the same way, tetrahydro-anhydro-thevetigenin, obtained by catalytic reduction, is converted by chromic acid into tetrahydro-anhydro-digitoxigenone, m.p. 284°, $[\alpha]_D$ + 37·3° ($CHCl_3$).

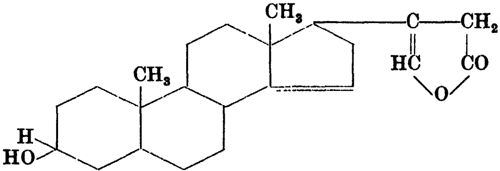
Digitoxin, $C_{41}H_{64}O_{13}$, m.p. 263°, $[\alpha]_D$ + 32·6°, one of the most active of the *Digitalis* substances, is hydrolysed by acids to digitoxigenin (I), $C_{23}H_{34}O_4$, m.p. 250°, $[\alpha]_D$ + 19°; acetyl derivative m.p. 217° (*Windaus* and *Stein*, Ber. **61**, 2436) and three mol. of digitoxose = desoxy-methyl-pentose, $C_6H_{12}O_4$. Isodigitoxigenin (II), m.p. 272° (acetyl deriv. m.p. 243°) is obtained by the general method for iso compounds (p. 528) (*Jacobs* and *Gustus*, J. Biol. Chem. **67** (1926), 333; **78** (1928), 576).



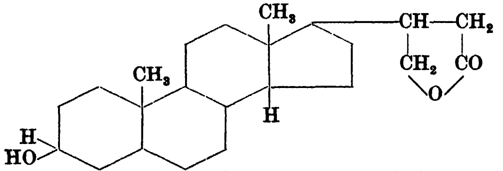
I. Digitoxigenin: $C_{23}H_{34}O_4$



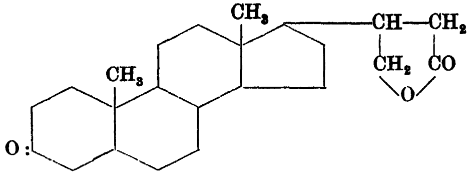
II. Iso-digitoxigenin: $C_{23}H_{34}O_4$



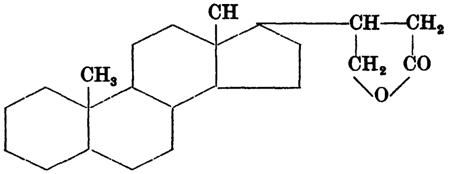
III. Anhydro-digitoxigenin: $C_{23}H_{32}O_3$



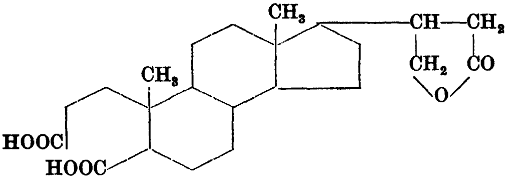
IV. Tetrahydro-anhydro-digitoxigenin: $C_{23}H_{36}O_3$



V. Tetrahydro-anhydro-digitoxigenone: $C_{23}H_{34}O_3$



VI. Lactone: $C_{23}H_{39}O_2$



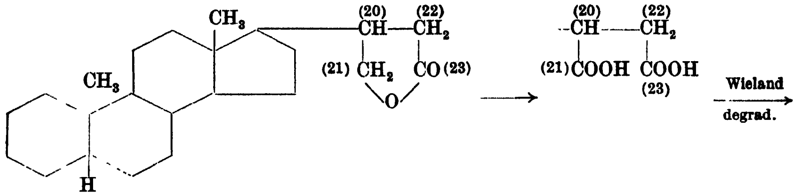
VII. Lactone-dicarboxylic acid: $C_{23}H_{34}O_6$

The tertiary hydroxyl group which takes part in this isomeric change is easily eliminated to give anhydro-digitoxigenin, (III), $C_{23}H_{32}O_3$, m.p. 193°, $[\alpha]_D - 4{\cdot}68°$ (methanol), in which there is no possibility of isomerisation. Tetrahydro-anhydro-digitoxigenin (IV), $C_{23}H_{36}O_3$, m.p. 168°, $[\alpha]_D + 24{\cdot}6°$ ($CH_3OH+CHCl_3$) is prepared by the catalytic reduction of anhydro-digitoxigenin.

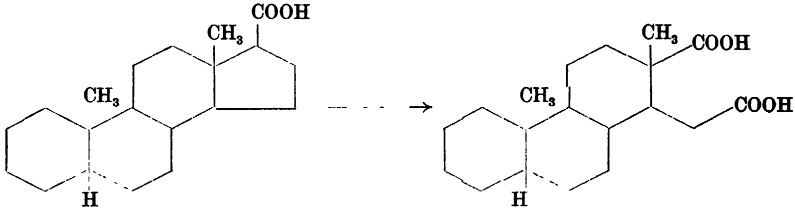
The fourth oxygen atom is present as a secondary alcohol group in ring A; mild oxidation with CrO_3 yields a ketone, **digitoxigenone**, $C_{23}H_{32}O_4$, m.p. 200°, $[\alpha]^{16}_{D} + 33{\cdot}3°$ (*Jacobs*, J. Biol. Chem. **67** (1926), 333; *Windaus* and *Stein*, Ber. **61**, 2440). In the same way, tetrahydro-anhydro-digitoxigenin (see above) gives with CrO_3 tetrahydro-anhydro-digitoxigenone (V), $C_{23}H_{34}O_3$, m.p. 245°, $[\alpha]_D + 37{\cdot}3°$ ($CHCl_3$) (*Windaus* and *Stein*, ibid. 2436). The same ketone is also obtained from tetrahydro-anhydro-thevetigenin (*Tschesche*, Ber. **69**, 2371). Clemmensen reduction of tetrahydro-anhydro-digitoxigenin (V) yields as the first product the hydroxyl-free lactone (VI), $C_{23}H_{36}O_2$, m.p. 185°, $[\alpha]^{16}_{D} + 33{\cdot}7°$ ($CHCl_3$) (*Windaus* and *Stein*, loc. cit.); this is the fundamental compound of the whole group. Energetic oxidation of the same ketone opens the 6-ring A to the lactone-dicarboxylic acid (VII), $C_{23}H_{34}O_6$, m.p. 296° (dimethyl ester m.p. 128°). Successive degradation of the lactone side-chain of digitoxigenin leads to aetiocholanic acid, $C_{20}H_{32}O_2$, m.p. 219° (*Jacobs* and *Elderfield*, J. Biol. Chem. **108** (1934), 497).

Uzarigenin, $C_{23}H_{34}O_4$ (formula p. 530), has been of particular importance in the development of the constitution of the *Digitalis* cardiac aglycones. Dehydrogenation of anhydro-uzarigenin with Se (*Tschesche*, Z. physiol. Chem. **222**, 58) gave the same hydrocarbon, $C_{18}H_{16}$, which was obtained by the similar reaction with a series of sterols and bile-acids (see p. 553: sterols). Soon afterwards *Tschesche* (ibid. **229**, 219; Ber. **68**, 7) oxidised away three C-atoms from the saturated lactone, $C_{23}H_{36}O_2$, prepared from uzarigenin, and obtained an acid $C_{20}H_{32}O_2$, which was identical with aetio-allo-cholanic acid, and could be oxidised further to aetio-allo-bilianic acid,

$C_{19}H_{30}O_4$. These reactions prove the presence of the tetracyclic sterol skeleton:



Sat. lactone from uzarigenin



Aetio-allo-cholanic acid: $C_{20}H_{32}O_2$ Aetio-allo-bilianic acid, $C_{19}H_{30}O_4$

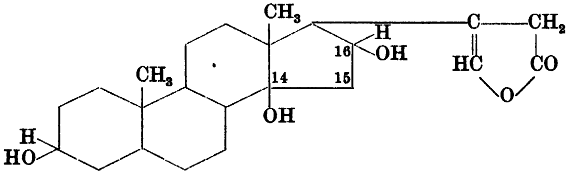
Uzarin, $C_{35}H_{54}O_{14}$, m.p. 270° $[\alpha]_D - 27°$ (pyridine), is the mild cardiac poison of the drug "uzara", which is obtained from the roots of an African species of *Gomphocarpus* (*Windaus* and *Haack*, Ber. **63**, 1377). Hydrolysis for four hours with 2% H_2SO_4 gives two mol. of glucose, but the uzarigenin, $C_{23}H_{34}O_4$, loses a tertiary hydroxyl group by dehydration and yields α- and β-anhydro-uzarigenin, $C_{23}H_{32}O_3$, m.p. 265°, $[\alpha]_D - 29{\cdot}5°$ (acetyl deriv. m.p. 175°), and m.p. 237°, $[\alpha]_D + 4{\cdot}9°$ (acetyl deriv. m.p. 168°). When reduced catalytically, the α-compound takes up two mol. of H_2 and gives α_1- and α_2-tetrahydro-anhydro-uzarigenin, $C_{23}H_{36}O_3$, m.p. 217°, $[\alpha]_D + 11{\cdot}3°$, and m.p. 230°, $[\alpha]_D + 20{\cdot}2°$. Oxidation of these leads to α_1- and α_2-tetrahydro-uzarigenone, $C_{23}H_{34}O_3$, keto-lactones of m.p. 249° and 217° resp., which can be reduced (Clemmensen) to the saturated lactones, $C_{23}H_{36}O_2$, α_1 m.p. 178°, α_2 m.p. 180°. The latter is distinct from the lactones from digitoxigenin and gitoxigenin, but identical with octahydro-trianhydro-periplogenin (*Tschesche*, Z. physiol. Chem. **222**, 52; *Jacobs* and *Bigelow*, J. Biol. Chem. **101** (1933), 697).

Energetic oxidation of the α_1- and α_2-keto-lactones opens ring A to give the lactone-dicarboxylic acids, $C_{23}H_{\ 4}O_8$, m.ps. 270° and 246°; these, like all dicarboxylic acids obtained by the fission of ring A, yield pyro-ketones on thermal decomposition (*Tschesche*, Z. physiol. Chem. **222**, 55).

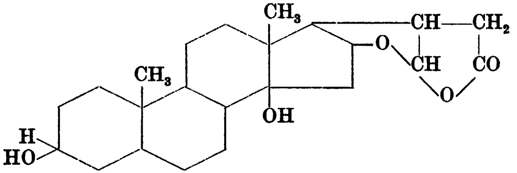
Dehydrogenation with Se (*Tschesche*, ibid., p. 58) yields the hydrocarbon, $C_{18}H_{16}$, m.p. 125–126° (picrate m.p. 122°), which was first obtained in the same way from cholesterol by Diels, and later from other sterols and bile-acid derivatives (see Sterols, p. 553).

Oxidation (*Tschesche*, Z. physiol. Chem. **229**, 230) of the α_1 and α_2 saturated lactones, $C_{23}H_{36}O_2$, (see above) with CrO_3 in acetic acid gives the dicarboxylic acid, $C_{23}H_{36}O_4$, m.p. 245° (methyl ester m.p. 161°, $[\alpha]^{17}_D + 4{\cdot}9°$ ($CHCl_3$)), and then aetio-allo-cholanic acid, $C_{20}H_{\ 2}O_2$, m.p. 228–230° (methyl ester m.p. 140–142°, $[\alpha]^{19}_D + 48{\cdot}3°$); this is identical (*Tschesche*, Ber. **68**, 7) with the aetio-allo-cholanic acid prepared from hyodesoxy-cholanic acid (*Windaus* and *Bohne*, Ann. **433**, 278). Aetio-allo-bilianic acid, $C_{19}H_{30}O_4$, m.p. 265° decomp., is obtained by further degradation (Wieland degradation) of the aetio-allo-cholanic acid (*Tschesche*, Z. physiol. Chem. **229**, 231).

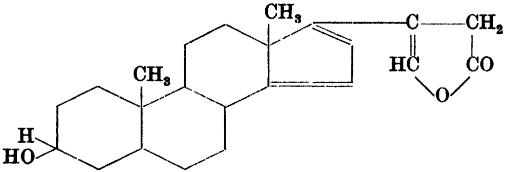
Gitoxigenin, $C_{23}H_{34}O_5$, is an unsaturated trihydroxy-lactone and a structural isomer of sarmentogenin and digoxigenin. Isogitoxigenin can be converted into a derivative of digitoxigenin (*Jacobs* and *Gustus*, J. Biol. Chem. **86** (1933), 199), and hence it contains a secondary hydroxyl group in the 3-position. In its reactions, gitoxigenin shows some differences from the other *Digitalis* aglycones. It appears to resemble them in giving an iso-compound, but the tertiary OH on C_{14} does not take part in the change: instead, a secondary OH on C_{16} comes into play, because isogitoxigenin is readily dehydrated (in contrast to the other iso-compounds), and this fact shows that the tertiary OH on C_{14} is still intact (II). The fact that gitoxigenin loses two mol. of water when boiled with acids is also important, for the dianhydro-gitoxigenin (III) so formed, which contains 3 double bonds, is identical with digitaligenin (*Windaus* and *Haack*, Ber. **62**, 475).



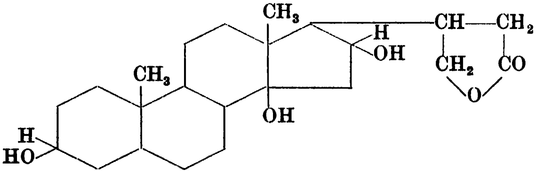
I. Gitoxigenin



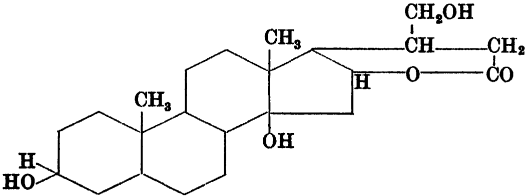
II. Iso-gitoxigenin



III. Dianhydro-gitoxigenin



IV. α-Dihydro-gitoxigenin



IVa. β-Dihydro-gitoxigenin.

The position of the second hydroxyl group on C_{16} is also disclosed by the fact that by catalytic reduction of gitoxigenin *Windaus* (Ber. **61**, 1850) obtained two pure dihydro-derivatives, the origin of which can only be explained by a lactonisation to the OH on C_{16}, as shown in formulae (IV) and (IVa). In agreement with this conclusion, both dihydro-gitoxigenins are hydrolysed to the same dihydro-gitoxigenic acid (*Jacobs* and *Elderfield*, J. Biol. Chem. **100** (1933), 671).

Gitoxin (bigitalin), $C_{41}H_{64}O_{14} \cdot H_2O$, m.p. 285°, $[\alpha]_D + 3{\cdot}5°$, is an enzymatic hydrolyis product of the true glycoside digilanide B from *Digitalis lanata*, and of purpurea-glycoside B from the leaves of *Digitalis purpurea* (*Stoll*, Helv. **16**, 1052; **17**, 592); it is obtained technically as a by-product in the preparation of digitoxigenin. It was first prepared pure by *Windaus* and *Schwarte* (Ber. **58**, 1515). Acid hydrolysis yields three mol. of digitoxose (a desoxy-methyl-pentose, $C_6H_{12}O_4$), and **gitoxigenin** (=hydroxy-digitoxigenin; see p. 533) $C_{23}H_{34}O_5$, m.p. 235°, $[\alpha]_D + 32{\cdot}6°$ (diacetate m.p. 250°). Gitoxigenone m.p. 207°; isogitoxigenin m.p. 252° (from alc.); isogitoxigeninic acid, $C_{23}H_{36}O_6$, m.p. 149° (from alc.) (*Jacobs* and *Gustus*, J. Biol. Chem. **79** (1928), 553; **82**, 403). Oxidation of isogitoxigenin gives isogitoxigenone, $C_{23}H_{32}O_5$, m.p. 279°, isogitoxigenic acid, $C_{23}H_{34}O_6$, m.p. 260°, $[\alpha]_D - 50°$, and isogitoxigonic acid, $C_{23}H_{32}O_6$ (methyl ester m.p. 174°) (*Jacobs* and *Gustus*, J. Biol. Chem. **82** (1933), 403). The two isomeric dihydro-gitoxigenins, $C_{23}H_{36}O_5$, α, m.p. 212°, β, m.p. 241°, $[\alpha]_D^{20} - 48{\cdot}74°$ (CH_3OH), are obtained by catalytic reduction (*Windaus*, Ber. **61**, 1850), and on hydrolysis of the lactone ring they yield the same dihydro-gitoxigenic acid, $C_{23}H_{38}O_6$. With alcoholic HCl, both dihydro-gitoxigenins give dianhydro-dihydrogitoxigenin, $C_{23}H_{32}O_3$, m.p. 166°; reduction of the two double bonds of this compound gives hexahydro-dianhydro-gitoxigenin (hexahydro-digitaligenin $C_{23}H_{36}O_3$, m.p. 214°, $[\alpha]_D^{20} + 75{\cdot}7°$ (alc.) (acetyl deriv. m.p. 155°) (*Windaus*, *Westphal* and *Stein*, Ber. **61**, 1851). Oxidation with CrO gives the corresponding ketone, hexahydro-dianhydro-gitoxigenone (hexahydro-digitaligenone), $C_{23}H_{34}O_3$, m.p. 207°, $[\alpha]_D + 85{\cdot}9°$ ($CHCl_3$); further oxidation leads to the dicarboxylic acid, $C_{23}H_{34}O_6$, m.p. 282°, $[\alpha]_D^{20} + 100°$ (AcOH) (dimethyl ester m.p. 163°, $[\alpha]_D^{20} + 82{\cdot}3°$ ($CHCl_3$)), which by distillation in high vacuum yields a pyro-ketone, $C_{22}H_{32}O_3$, m.p. 206°, (oxime m.p. 248°); this shows that the 6-ring A has been opened. Hexahydro-dianhydro-gitoxigenone can be reduced by Clemmensen's method to the saturated lactone, $C_{23}H_{36}O_2$ (*Windaus* and *Bandte*, Ber. **56**, 2004).

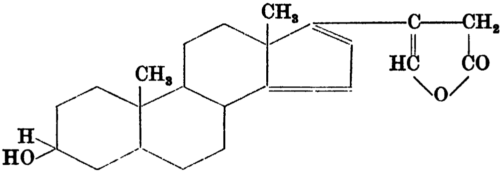
Gitalin, $C_{35}H_{56}O_{12} + {}^1/_2 H_2O$, m.p. 155°, $[\alpha]_D - 25{\cdot}2°$, is a glycoside first obtained from *Digitalis purpurea* by *Cloetta* (C. 1926 II 771). A possible formula has been suggested by *Windaus* (C. 1929 I 247); he has shown that acid hydrolysis of the glycoside gives two mol. of digitoxose and gitaligenin, $C_{23}H_{36}O_6$, m.p. 222°, $[\alpha]_D^{20} + 31{\cdot}23°$, which is probably a hydrate of gitoxigenin.

Digitalin, $C_{36}H_{56}O_{14}$, m.p. 229°. $[\alpha]_D + 14{\cdot}2°$, was discovered by *Dulong* in 1827 in the seeds of *Digitalis purpurea*, and has been investigated by *Kiliani* (Ann. **230**, 250; Ber. **31**, 2460; Arch. Pharm. **252** (1914), 26) and later by *Windaus* (Ber. **56**, 2001; **57**, 1386); **oleandrin,** $C_{30}H_{46}O_9$, m.p. 249°, is found in the leaves of *Nerium Oleander*. Both compounds have the same aglycone, **digitaligenin,** $C_{23}H_{30}O_3$, m.p. 213°, $[\alpha]_D + 56{\cdot}9°$, which in the former is combined with glucose and digitalose, $C_7H_{14}O_5$ (*Kiliani*, Arch. Pharm. **230** (1892), 250; Ber. **31**, 2461; **63**, 2866), and in the latter only with digitalose (*Windaus* and *Westphal*, C. 1926 I 1814).

Digitaligenin, $C_{23}H_{30}O_3$ (acetyl deriv. m.p. 208°), is a hydroxy-lactone with three double bonds, and gives on catalytic reduction a tetrahydro-compound, $C_{23}H_{34}O_3$, m.p. 194° (acetyl deriv. m.p. 168°), and a hexahydro-compound, $C_{23}H_{36}O_3$, m.p. 214° (acetyl deriv. m.p. 155°). The action of CrO_3 upon the latter leads to hexahydro-digitaligenone, $C_{23}H_{34}O_3$, m.p. 207° and further to the dicarboxylic acid $C_{23}H_{34}O_6$, m.p. 287° (dimethyl ester m.p. 174°) (*Windaus*, C. 1928 II 669).

Hexahydro-digitaligenin is identical with hexahydro-dianhydrogitoxigenin (above; see formula, p. 534), from which it follows that digitaligenin is

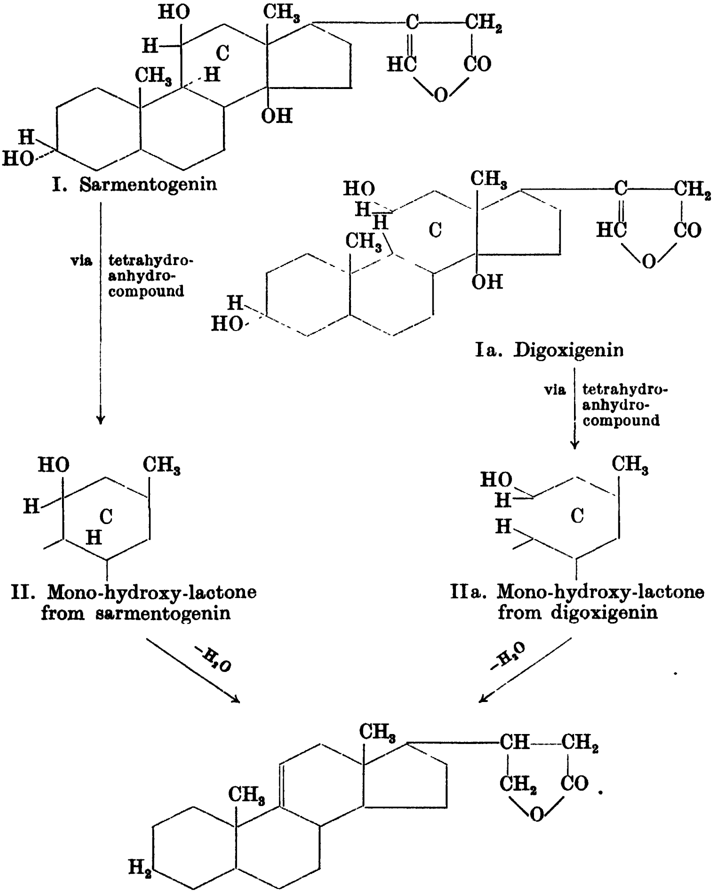
dianhydrogitoxigenin; gitoxigenin is converted into digitaligenin by alcoholic HCl (*Windaus, Westphal* and *Stein,* Ber. 61, 1849).



Digitaligenin

The conjugation of the double bonds is in good agreement with the ultraviolet absorption (*Tschesche,* Erg. d. Physiol. 38 (1936), 48).

Digoxigenin, $C_{23}H_{34}O_5$ (Ia) and **sarmentogenin,** $C_{23}H_{34}O_5$ (I), are stereoisomeric trihydroxy-lactones of the cholane group. Of the three hydroxyl



I. Sarmentogenin

Ia. Digoxigenin

II. Mono-hydroxy-lactone from sarmentogenin

IIa. Mono-hydroxy-lactone from digoxigenin

III. Dehydro-lactone.

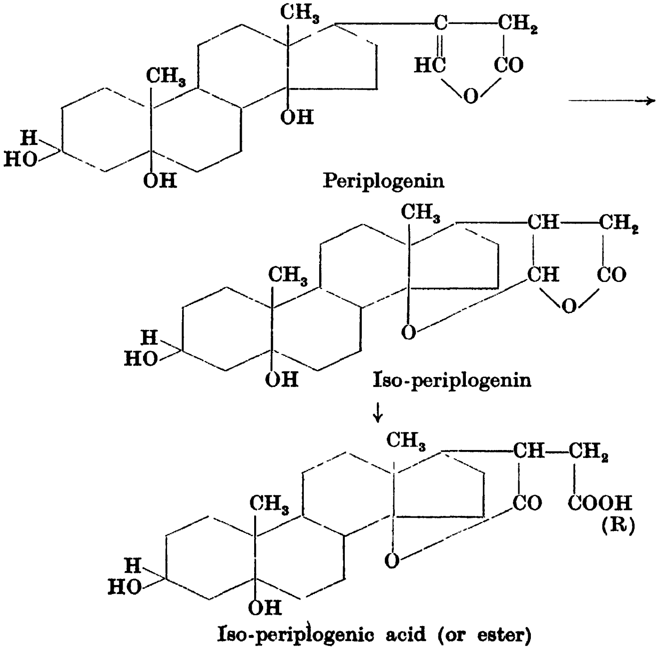
groups, two are secondary (formation of diketones), and one is tertiary. The latter is at C_{14}, as in all the genins, and is recognised by the usual reactions, the easy conversion of both aglycones into iso-compounds, and the elimination of water during energetic acid hydrolysis, giving anhydro-sarmentogenin and anhydro-digoxigenin. One of the secondary hydroxyls is at C_3 (oxidation to dicarboxylic acids, which form pyro-ketones on high-vacuum distillation). Neither digoxigenin nor sarmentogenin are precipitated by digitonin in alcoholic solution; hence the OH on C_3 and the CH_3 on C_{10} are in the trans position to one another in respect to ring A. In both genins the second hydroxyl group is on C_{11}, and hence they are stereoisomers (*Tscheshe* and collaborators, Ber. **69**, 794, 2499). Tscheshe has confirmed this conclusion by converting the two compounds into the same derivative in the following way: oxidation of tetrahydro-anhydro-sarmentogenin gives tetrahydro-anhydro-sarmentogenone, a diketo-lactone; the ketone group at C_3 in the latter can be removed by mild reduction, and the mono-keto-lactone so obtained (CO at C_{11}) can be reduced catalytically to the corresponding mono-hydroxy-lactone (II). Dehydration converts this into an unsaturated dehydro-lactone (III), which is identical with the dehydro-lactone prepared by the similar steps (IIa, III) from digoxigenin. Sarmentogenin and digoxigenin are stereoisomeric in the arrangement about C_9, since they give identical derivatives as soon as the asymmetry at C_9 is destroyed. (See p. 536.)

Digoxin, $C_{41}H_{64}O_{14}$, m.p. 265°, $[\alpha]_D + 13{\cdot}3°$, the product of the enzymatic hydrolysis of digilanide C (see p. 528), was first isolated in 1930 from the leaves of *Digitalis lanata* (*Smith*, J. **1930**, 508, 2478; **1935**, 1305; **1936**, 354), together with other cardiac poisons which are also found in *Digitalis purpurea*. Hydrolysis gives three mol. of digitoxose and **digoxigenin,** $C_{23}H_{34}O_5$, m.p. 222°, $[\alpha]_D + 27°$ (isolation by the hydrolysis of digilanide: *Tscheshe* and *Bohle*, Ber. **69**, 793); diacetyl deriv. m.p. 221°; dihydro-digoxigenin m.p. 215°; digoxigenone (diketone), $C_{23}H_{30}O_5$, m.p. 265°, $[\alpha]^{20}_{5461} + 130°$ (acetone); isodigoxigenin, $C_{23}H_{34}O_5$, m.p. 260° decomp., from digoxigenin and methyl alcoholic KOH; isodigoxigenone (diketone), $C_{23}H_{30}O_5$, m.p. 335°, from isodigoxigenin and CrO_3; isodigoxigeninic acid, $C_{23}H_{36}O_6$, m.p. 228° decomp.: methyl ester m.p. 145°. Anhydro-digoxigenin, $C_{23}H_{32}O_4$: α, m.p. 192°, $[\alpha]^{20}_{5461} + 46°$ (CH_3OH); β, m.p. 182°, $[\alpha]^{20}_{5461} - 16{\cdot}3°$ (CH_3OH) (*Smith*, loc. cit.). Anhydro-digoxigenone, m.p. 260°. Tetrahydro-anhydro-digoxigenin, $C_{23}H_{36}O_4$, is prepared by catalytic reduction of anhydro-digoxigenin (*Tscheshe* and *Bohle*, Ber. **69**, 795), and is oxidised by CrO_3 to tetrahydro-anhydro-digoxigenone (diketone), $C_{23}H_{32}O_4$, m.p. 290°; both the keto-groups (on C_3 and C_{11}) are reduced by Clemmensen's method to give the saturated lactone, $C_{23}H_{26}O_2$, m.p. 185°, $[\alpha]^{20}_D + 35{\cdot}4°$ ($CHCl_3$), which was first prepared from digitoxigenin (above) and later from gitoxigenin and sarmentogenin (*Tscheshe*, loc. cit.). Energetic oxidation of tetrahydro-anhydro-digoxigenone with CrO_3 opens ring A to give the keto-lactonic-dicarboxylic acid, $C_{23}H_{32}O_7$, m.p. 306° (dimethyl ester m.p. 160°), which, when heated with acetic anhydride, gives a pyro-ketone $C_{22}H_{30}O_4$, m.p. 228–229° (*Tscheshe*, loc. cit.). For the preparation of the dehydro-lactone, $C_{23}H_{34}O_2$, m.p. 174–175°, $[\alpha]^{18}_D + 35{\cdot}5°$ ($CHCl_3$), and its comparison with compounds from sarmentogenin, see *Tscheshe* and *Bohle* (Ber. **69**, 2503).

Sarmentocymarin, $C_{30}H_{46}O_8$, m.p. 165° (anhyd.), $[\alpha]_D - 12{\cdot}2°$, is obtained from the seeds of *Strophanthus sarmentosus* (*Jacobs* and *Heidelberger*, J. Biol. Chem. **81** (1929), 765; *Tscheshe* and *Bohle*, Ber. **69**, 2500). On hydrolysis it yields sarmentose, $C_7H_{14}O_4$, m.p. 79°, which is the methyl ether of a desoxy-sugar, and **sarmentogenin,** $C_{23}H_{34}O_5$, m.p. 270°, $[\alpha]_D + 21{\cdot}3°$ (alcohol); dibenzoyl deriv. m.p. 281°, $[\alpha]^{20}_D + 14°$ (acetone). Dihydro-sarmentogenin, $C_2\ H_{36}O_5 + C_2H_5OH$, has m.p. 142° decomp.; sarmentogenone, $C_{23}H_{32}O_5$, m.p. 226° (semicarbazone m.p. 200° decomp.), is prepared by oxidation of sarmentogenin with CrO_3 in acetic acid. Energetic hydrolysis eliminates a tertiary hydroxyl group as water, to form two anhydro-sarmentogenins, $C_{23}H_{32}O_4$: α, m.p. 208°, $[\alpha]^{21}_D - 27{\cdot}7°$ ($CHCl_3$) (*Tscheshe*, Ber. **68**, 423), β, m.p.

243° (*Jacobs* and *Heidelberger*, J. Biol. Chem. **81** (1929), 765). The reduction of both double bonds of α-anhydro-sarmentogenin leads to α-tetrahydro-anhydro-sarmentogenin, $C_{23}H_{36}O_4$, m.p. 120°, [α]$^{20}_{D}$ + 11° ($CHCl_3$), which is oxidised in the cold by CrO_3 in acetic acid to a diketone, α_1-tetrahydro-anhydro-sarmentogenone, $C_{23}H_{32}O_4$, m.p. 270°, [α]$^{21}_{D}$ + 47·5°; in this compound the two secondary hydroxyls have been converted into keto-groups. This diketone links together sarmentogenin and digitoxigenin. By reduction of both keto-groups (in an indirect manner, see *Tschesche* and *Bohle*, Ber. **69**, 2498) of α_1-tetrahydro-anhydro-sarmentogenone, the same saturated lactone, $C_{23}H_{36}O_2$, m.p. 189°, [α]$^{20}_{D}$ + 35·4° ($CHCl_3$), is formed as that obtained from digitoxigenin, which contains one OH less (*Windaus* and *Stein*, Ber. **61**, 2436; *Tschesche* and *Bohle*, Ber. **69**, 2503). Under somewhat milder conditions tetrahydro-anhydro-sarmentogenone, $C_{23}H_{32}O_4$, loses only the keto-group at C_3, to form a mono-keto-lactone, $C_{23}H_{34}O_3$: from α_1, m.p. 162°, [α]$^{16}_{D}$ + 25·5° ($CHCl_3$); from α_2, m.p. 193°, [α]$^{16}_{D}$ + 44·6° ($CHCl_3$), which can be reduced catalytically to a mono-hydroxy-lactone, $C_{23}H_{36}O_3$ (formula IIa, p. 536): from α_1, m.p. 228°, from α_2, m.p. 208°, [α]$^{16}_{D}$ + 49·5° ($CHCl_3$). The mono-hydroxy-lactone from α_2 loses water on distillation with potassium bisulphate to give a dehydro-lactone, $C_{23}H_{34}O_2$ (formula III, p. 536), m.p. 175°, [α]$^{18}_{D}$ + 35·5° ($CHCl_3$), identical with the compound prepared in a similar way from digoxigenin (*Tschesche* and *Bohle*, Ber. **69**, 2502).

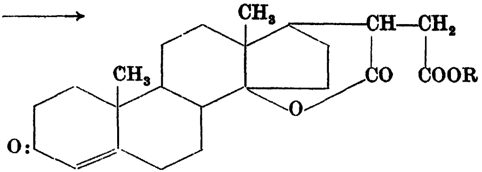
Periplogenin, $C_{23}H_{34}O_5$, forms a link between the *Digitalis* glycosides and strophanthidin which is discussed later. Strophanthidin can be converted by an unambiguous series of reactions into isoperiplogenic acid (see p. 540), which is readily obtained by the oxidation of isoperiplogenin (*Jacobs* and collaborators, J. Biol. Chem. **91** (1931), 617). Again, the ester of isoperiplogenic acid can be converted, as shown in the following formulae (elimination of OH on C_5), into a derivative of digitoxigenin, viz. iso-digitoxigonic ester; periplogenin is hence a 5-hydroxy-digitoxigenin.



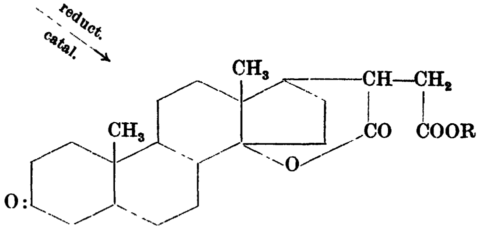
Periplogenin

Iso-periplogenin

Iso-periplogenic acid (or ester)



Anhydro-iso-periplogonic ester



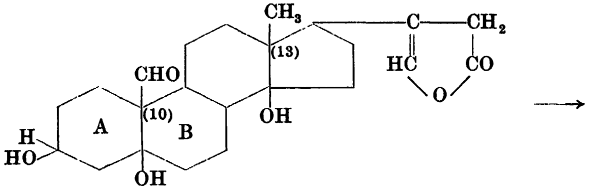
Iso-digitoxigonic ester

The position of the three hydroxyl groups on the cholane nucleus follows from the investigations of the structure of strophanthidin which are described later.

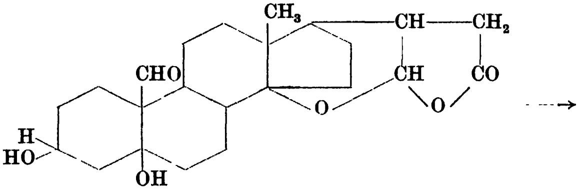
Periplocin, $C\ _6H_{56}O_1 \cdot H_2O$, first prepared by *Lehmann* (Arch. Pharm. **235**, 161) from the bark of *Periploca graeca* (*Asclepiadaceae*), is hydrolysed by enzymes to **periplocymarin,** $C_{30}H_{46}O_8 \cdot CH_3OH$, m.p. 148°, $[\alpha]_D + 29°$ (95% alcohol), and *d*-glucose, while mineral acids hydrolyse the former into cymarose, $C_7H_{14}O_4$, and **periplogenin,** $C_{23}H_{34}O_5$, $[\alpha]_D^{27} + 31{\cdot}5°$ (alcohol) (the m.p. is indefinite; benzoyl deriv. m.p. 235°). Dihydro-periplogenin, $C_{23}H_{36}O_5$, has m.p. 204°; isoperiplogenin, $C_{23}H_{34}O_5$, m.p. 258°, is prepared from periplogenin with methyl alcoholic alkali. Isoperiplogenic acid, $C_{23}H_{34}O_6$, m.p. 217° (gas evol.), methyl ester m.p. 222°, is obtained by the oxidation of isoperiplogenin with hypobromite (*Jacobs* and *Hoffmann*, J. Biol. Chem. **79** (1928), 519). Isoperiplogenic acid is also obtained from isostrophanthidic acid (below) by reduction of the $-CHO$ group into $-CH_3$ via the semicarbazone (see strophanthidin; *Jacobs*, *Elderfield*, *Grave* and *Wignall*, J. Biol. Chem. **91** (1931), 617; *Jacobs* and *Elderfield*, ibid. **91** (1931), 625). Periplogenin is therefore desoxo-strophanthidin. Trianhydro-periplogenin, $C_{23}H_{28}O_2$, m.p. 193°, $[\alpha]_D^{24} - 130°$ (pyridine), prepared by boiling periplogenin with methyl alcoholic HCl, takes up $4H_2$ catalytically, and gives octahydro-trianhydro-periplogenin, $C_{23}H_{36}O_2$, m.p. 177°, $[\alpha]_D^{25} + 16{\cdot}4°$ ($CHCl_3$) (*Jacobs* and *Bigelow*, J. Biol. Chem. **101** (1933), 697); this saturated lactone is identical with one prepared from uzarigenin (*Tschesche*, Z. physiol. Chem. **222**, 52).

Strophanthidin, $C_{23}H_{32}O_6$. The investigation of strophanthidin, and particularly the work of *Jacobs* and (in part) *Elderfield* (1st paper: J. Biol. Chem. **54** (1922), 253; 35th paper, J. Biol. Chem. **113** (1936), 631) has been one of the most important stages in the development of the chemistry of the vegetable cardiac glycosides. Jacobs obtained (Science **79** (1934), 279; J. Biol. Chem. **107** (1934), 143) Diels' hydrocarbon $C_{18}H_{16}$, 3-methyl-cyclopentenophenanthrene, by dehydrogenation of this genin with Se, and hence proved that the *Strophanthus* glycosides belonged to the cholane group. The formation of an iso-compound (see p. 528), and the ready elimination of one mol. of water, indicate a tertiary OH on C_{14}, and the remaining oxygen atoms have been shown to be present as a secondary OH (oxidation to keto-group), another tertiary OH, the lactone group and an aldehyde group (oxime; oxidation to acid, *Jacobs* and *Collins*, J. Biol. Chem. **65** (1925), 491). The position of the secondary OH is given by the relationship between strophanthidin and digitoxigenin (see p. 531); it must consequently be in the 3-position in ring A. The second tertiary OH must be in the β-position to the secondary OH in ring A, because it is readily eliminated as water as soon as the secondary OH is oxidised to a keto-group, a characteristic behaviour of β-hydroxy-ketones (*Jacobs* and *Gustus*, J. Biol. Chem. 74 (1927), 795). A similar hydroxyl group which behaves in exactly the same way is present in periplogenin, from which strophanthidin differs only in containing an aldehyde group in place of one methyl group.

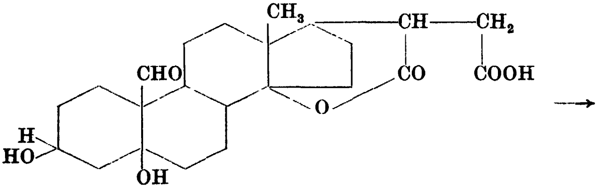
If in α-iso-strophanthidic acid (the oxidation product of iso-strophanthidin with hypobromite) the aldehyde group is reduced to a methyl group by the Wolff-Kishner method via the semicarbazone, iso-periplogenic acid is obtained, as is shown in the following formulae.



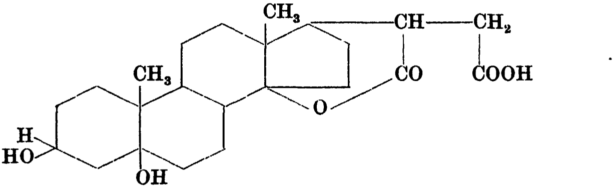
Strophanthidin



Iso-strophanthidin



Iso-strophanthidic acid



Iso-periplogenic acid

Iso-periplogenic acid can be converted into iso-digitoxonic acid (see periplogenin), a fact which shows clearly the connection between strophanthidin and digitoxigenin.

Only two positions for the aldehyde group need be considered, viz. C_{10} or C_{13} (see formula). The facts that this group is able to react both with the secondary OH in ring A (formation of cyclo-acetals: see *Jacobs* and *Collins*, J. Biol. Chem. **59** (1924), 713) and with the tertiary OH on C_{14} (pseudo-strophanthidin series), indicate that the aldehyde group is at C_{10}. Hence strophanthidin has the above formula, which was first proposed by *Kon* (Chem. and Ind. **58** (1934), 593, 956) on the basis of the experimental results of Jacobs and Tschesche and of the dimensions of the unit cell in the crystal of the substance (*Bernal* and *Crowfoot*, ibid. p. 953).

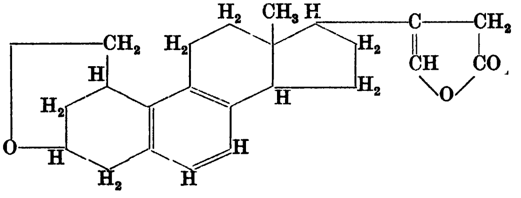
As regards the stereochemical configuration of strophanthidin, *Tschesche* and *Bohle* (Ber. **69**, 2443) conclude from considerations of the spatial model, that the rings A and B are joined in the cis position, as in most cardiac aglycones and in the bile-acids.

k-**Strophanthin,** $C_{36}H_{54}O_{14}$, $3H_2O$, m.p. 178 , $[\alpha]_D + 10°$, from *Strophanthus Kombé*, is hydrolysed by the enzyme strophanthobiase into **cymarin,** $C_{30}H_{44}O_9$, (decomp. 130–138°), $[\alpha]_D + 23{\cdot}5°$, and glucose (*Windaus* and *Hermanns*, Ber. **48**. 979; *Jacobs*, J. Biol. Chem. **69** (1926), 153). Further hydrolysis with dilute HCl leads finally to cymarose, $C_7H_{14}O_4$, and k-**strophanthidin** (cymarigenin), $C_{23}H_{32}O_6 \cdot 1^1/_2H_2O$, m.p. 175°, $[\alpha]_D + 43°$ (CH_3OH): monobenzoyl deriv. m.p. 230°, oxime m.p. 275 , dihydro-compound m.p. 195°, $[\alpha]_D + 34{\cdot}8°$ (CH_3OH).

Iso-strophanthidin, m.p. 276°, $[\alpha]_D + 36{\cdot}2°$ (CH_3OH), is oxidised by hypobromite to iso-strophanthidic acid, $C_{23}H_{32}O_7$, m.p. 233°, which can be converted by the Wolff-Kishner reduction into iso-periplogenic acid (*Jacobs*, J. Biol. Chem. **91** (1931), 617). Permanganate oxidises the aldehyde group of iso-strophanthidin to give iso-strophanthidinic acid, $C_{23}H_{32}O_7$, m.p. 234°.

The action of alcoholic HCl upon strophanthidin leads, via semi-acetals, to dehydration products (*Jacobs* and *Collins*, J. Biol. Chem. **59** (1924), 713; **63** (1925), 123). Anhydro-strophanthidin, $C_{23}H_{30}O_5 \cdot 2H_2O$, m.p. 223–226° (gas evol.) $[\alpha]^4_D - 145°$ (95% alcohol); oxime m.p. 260–265°; acetyl deriv. m.p. 294°. Dianhydro-strophanthidin, $C_{23}H_{28}O_4$, m.p. 236°, $[\alpha]^4_D - 222°$ ($CHCl_3$); oxime m.p. 281°, $[\alpha]^{25}_D - 174°$ (pyridine); acetyl derivative m.p. 206°, $[\alpha]^4_D - 222°$ ($CHCl_3$). Trianhydro-strophanthidin, $C_{23}H_{26}O_3$, m.p. 137·5°, $[\alpha]^{21}_D + 98°$ ($CHCl_3$).

While dianhydro-strophanthidin can be reduced catalytically, trianhydro-strophanthidin absorbs only one H_2, which saturates the double bond of the lactone side-chain, and the remaining three double bonds are not hydrogenated. Hence trianhydro-strophanthidin contains a benzene nucleus, in agreement with its strong absorption in the ultraviolet (*Jacobs* and *Collins*, J. Biol. Chem. **63** (1925), 123; **106** (1934), 71). Since trianhydro-strophanthidin does not form an oxime or a phenyl-hydrazone, it is given the following formula by *Jacobs* and *Elderfield* (J. Biol. Chem. **108** (1935), 693):

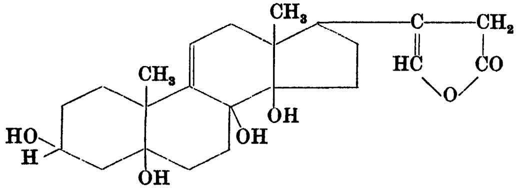


Trianhydro-strophanthidin

Oxidation of trianhydro-strophanthidin with conc. HNO_3 (*Tschesche* and *Knick*, Z. physiol. Chem. **229** (1934), 233) gives mellophanic acid (benzene-1:2:3:4-tetracarboxylic acid), which is further experimental support for the above formula. Ring B can only become aromatic when the aldehyde group wanders from C_{10} to C_1.

Another strophanthin has been isolated from *Strophanthus hispidus*; this is hydrolysed firstly to cymarin and glucose, and then further to strophanthidin and cymarose. Probably a different glucosidocymarose is present in this substance (*Jacobs* and *Hoffmann*, J. Biol. Chem. **79** (1928), 531).

Convallatoxigenin, $C_{23}H_{32}O_6$, is the aglycone of **convallatoxin**; it is the most powerful cardiac poison yet known and is found in the lily of the valley. The aglycone, in contrast to those of the *Digitalis* cardiac poisons, has two double bonds, one in the $\beta\gamma$-unsaturated lactone group (positive Legal test), and a second which is remarkable for its resistance to hydrogenation. Of the hydroxyl groups one is probably secondary and the other three tertiary. One of the latter is at C_{14} (as in the *Digitalis* aglycones), since convallatoxigenin readily gives iso-compounds. *Tschesche* and *Haupt* (Ber. **69**, 461) give the following tentative formula for this genin:



Convallatoxigenin.

Convallatoxin, $C_{29}H_{42}O_{10}$, m.p. 239° (hydrated), m.p. 225° (anhyd.), is extracted from the leaves of the lily of the valley (*Convallaria majalis* L.) (*Karrer*, Helv. **12**, 506). It is undergoes isomeric change with alcoholic alkali and gives two iso-compounds: α-isoconvallatoxin, m.p. 258°, and the β-compound m.p. 290°, both of which give a negative Legal test (*Tschesche* and *Haupt*, Ber. **69**, 462). Hydrolysis with alcoholic sulphuric acid yields, not the true genin, convallatoxigenin, $C_{23}H_{32}O_6$, but, because of the ease of elimination of one mol. of water, its anhydro-compound, $C_{23}H_{30}O_5$; this can, however, only be obtained crystalline in the form of its benzoate (m.p. 281°, $[\alpha]_D + 22{\cdot}2°$ [$CHCl_3$]). The sugar component has been identified as rhamnose (phenylosazone, m.p. 182°; p-nitrophenylosazone, m.p. 250°) (*Tschesche* and *Haupt*, Ber. **69**, 464).

Antiarigenin is the aglycone of the cardiac poison of "ipooh" which is used as an arrow-poison and is obtained from the milky sap of the Indian upas tree *Antiaris toxicaria* (*Rosenthaler*, C. 1925 I 1226; *Möller* and *Pribyl*, C. 1930 II 1564). The sap yields two **antiarins,** $C_{29}H_{42}O_{11}$: α-compound m.p. 225°, oxime m.p. 240°; β-compound m.p. 208°. The genin of these glycosides, **antiarigenin,** $C_{23}H_{32}O_7$, is combined with antiarose, $C_6H_{12}O_5$, in the α-compound and with *l*-rhamnose, $C_6H_{12}O_5$, in the β-compound, but cannot be isolated. Acid hydrolysis yields dianhydro-antiarigenin (*Kiliani*, Ber. **48**, 3574; **46**, 667, 2179; *Tschesche* and *Haupt*, Ber. **69**, 1377) $C_{23}H_{28}O_5$, m.p. 165–167° or 200–205°, $[\alpha]^{20}_{D} - 160{\cdot}2°$ ($CHCl_3$); benzoyl deriv. m.p. 249–250°. One oxygen atom of antiarigenin is present as an aldehyde group (cf. oxime, above). Antiarigenin is probably a hydroxy-strophanthidin (*Tschesche*, loc. cit.), but its constitutional formula is not yet known with certainty. This is also true for

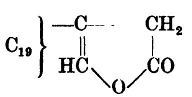
Ouabagenin, $C_{23}H_{34}O_8$, (g-strophanthidin), the aglycone of **ouabain** (g-strophanthin), $C_{29}H_{44}O_{12}$, m.p. 188°, $[\alpha]_D - 30°$, a South American arrow-poison from *Strophanthus glaber* and *gratus* and from the bark of the ouaba-tree (*Jacobs* and *Bigelow*, J. Biol. Chem. **96** (1932), 647). Catalytic reduction gives dihydro-ouabain, $C_{29}H_{46}O_{12}$, m.p. indefinite, $[\alpha]^{30}_{D} - 47{\cdot}4°$. Iso-ouabain, $C_{29}H_{44}O_{12}$, m.p. 213–215° decomp., $[\alpha]^{19}_{D} + 45{\cdot}7°$ (water), is obtained from ouabain and methyl alcoholic potash.

Ouabain is the rhamnoside of the tetracyclic hexahydroxy-$\beta\gamma$-unsaturated lactone **ouabagenin** (g-strophanthidin), $C_{23}H_{34}O_8$, and is only hydrolysed by acids with difficulty. Neither the genin nor the iso-genin has yet been obtained, because, under the vigorous conditions needed for hydrolysis, both compounds readily eliminate three mol. of water and one of formaldehyde. Thus acetylation of iso-ouabain with acetic anhydride and sulphuric acid leads to an acetyl-trianhydro-hydroxy-lactone, $C_{24}H_{28}O_5$, m.p. 244–246°, $[\alpha]_D^{22} - 22{\cdot}7^\circ$ (pyridine), which can be hydrolysed to the free lactone, $C_{22}H_{26}O_4$, m.p. 256–258°, $[\alpha]_D^{22} + 29{\cdot}1^\circ$ (pyridine). For a preliminary formula for ouabain, see *Fieser* and *Newman*, J. Biol. Chem. **114** (1936), 705; this is, however, by no means final (*Tschesche*, Ber. **70**, 43).

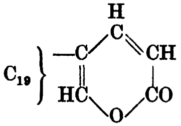
II. Vegetable Cardiac Poisons with an Aglycone of 24 C atoms

A new type of plant substance with cardiac action has been isolated from the squill (*Scilla maritima*, and *Bulbus scillae*); in contrast to the compounds already discussed, its aglycone contains 24 C atoms. These compounds bridge the gap between the other cardiac poisons and the substances with cardiac action secreted by the skin of toads, which also contain 24 C atoms in the molecule.

Scillaridin, the only aglycone of this class which has been investigated to any extent so far, gives no Legal test (see p. 529). It contains a lactone group, but this cannot contain a $\beta\gamma$-double bond. According to Stoll, it is a derivative of α-pyrone (cumalin), in which the mono-unsaturated 5-membered lactone ring of the *Digitalis* and *Strophanthus* aglycones is enlarged to a di-unsaturated 6-membered lactone ring.

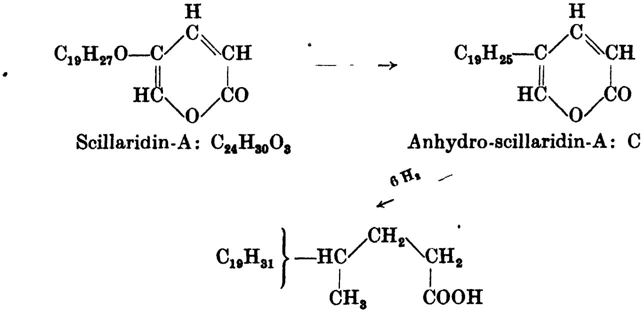


Digitalis and *Strophanthus*



Scillaridin

The evidence for this lactone side-chain rests on the conversion of scillaridin-A into allo-cholanic acid (*Stoll*, *Hofmann* and *Helfenstein*, Helv. **18**, 644), which also proves that the genin is derived from the cholane ring-system; the conversion is shown in the following formulae.

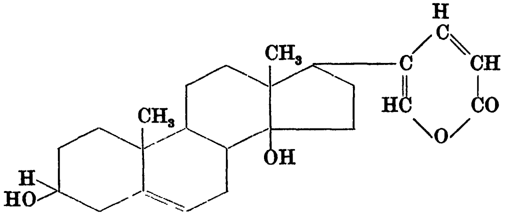


Scillaridin-A: $C_{24}H_{30}O_3$

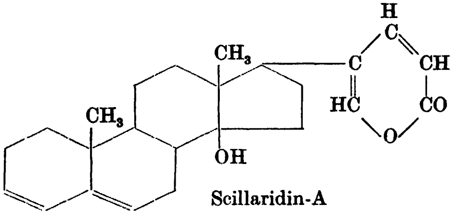
Anhydro-scillaridin-A: $C_{24}H_{28}O_2$

Allo-cholanic acid, $C_{24}H_{40}O_2$

Scillaren-A, $C_{36}H_{52}O_{13}$, m.p. 270°, $[\alpha]_D - 73{\cdot}8^\circ$, has been prepared pure from the squill (*Scilla maritima*) and investigated in detail (*Stoll* and collaborators, Helv. **16**, 703; **17**, 641, 1334; **18**, 82, 120, 401, 644, 1247). When the freshly minced squill is kept under ethyl acetate, the action of an enzyme, scillarenase, present in the plant produces one mol. of glucose and **pro-scillaridin-A,** $C_{30}H_{42}O_8$, m.p. 213°, $[\alpha]_D - 82{\cdot}6^\circ$ (*Stoll*, *Kreis* and *Hofmann*, Z. physiol. Chem. **222**, 24), while acid hydrolysis gives **scillaridin-A,** $C_{24}H_{30}O_3$, m.p. 245–250°, $[\alpha]_D - 62{\cdot}7^\circ$, and scillabiose, $C_{12}H_{22}O_{10}$, a disaccharide of rhamnose and glucose (*Stoll* and co-workers, Helv. **16**, 703). Scillaridin is the anhydro product of the true genin, scillagenin, $C_{24}H_{32}O_4$, which cannot be isolated. Scillaridin is an unsaturated hydroxy-lactone with four double bonds; its remaining hydroxyl group can be eliminated by high-vacuum distillation; this gives anhydro-scillaridin-A, $C_{24}H_{28}O_2$, which contains five double bonds. Exhaustive hydrogenation of this compound (6 H_2 absorbed) also reduces the lactone-ring, and gives a mixture of acids, $C_{24}H_{40}O_2$, from which can be isolated allo-cholanic acid (α-scillanic acid), m.p. 172–173°, $[\alpha]_D + 22{\cdot}5^\circ$ (dioxan) (see the bile-acids). As with the *Strophanthus* and *Digitalis* glycosides, scillaridin-A rearranges in presence of alcoholic alkali into derivatives of iso-scillaridin-A (*Stoll*, Helv. **17**, 641). The constitution of scillagenin and of scillaridin-A is not yet fully established; *Tschesche* and *Haupt* (Ber. **70**, 44) have put forward the following as the most probable formulae:

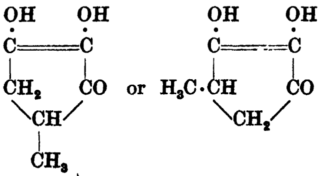


Scillagenin-A: $C_{24}H_{32}O_4$



Scillaridin-A

From the dried leaves and stalks of *Calotropis procera*, a poisonous tropical plant belonging to the *Asclepiadaceae*, *Hesse* and *Reicheneder* (Ann. **526**, 252) have isolated **calotropin,** $C\ _9H_{40}O_9$, m.p. 221° decomp., monohydrate $[\alpha]_D + 55{\cdot}7^\circ$ (CH_3OH). Methyl-calotropin, amorphous, m.p. 165°, is obtained by the action of ethereal diazomethane. Prolonged boiling with alcoholic HCl only gives anhydro-calotropin, $C_{29}H_{38}O_8$, m.p. 207°, and the genin cannot be obtained. This behaviour, which is quite different from that of the cardiac poisons already considered, shows that calotropin is a cardiac poison of a new type. The thermal decomposition of calotropin at 230° in high vacuum provides valuable evidence of the structure: the products are methyl-reductic acid (I), $C_6H_8O_3$, m.p. 84° (dinitro-phenyl-osazone m.p. 230° decomp.), which is sensitive to oxygen and a strong reducing agent, and **calotropagenin,** $C_{23}H_{32}O_6$, m.p. 240°, $[\alpha]_D + 42^\circ$ (CH_3OH), which gives a positive Legal test and can be isolated in small quantities from the drug itself.

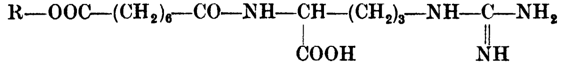


I. Methyl-reductic acid

Two of the oxygen atoms of the genin are in the enolic lactone group, and two more are present as hydroxyls; by analogy, one of these is placed on C_3. Iso-calotropagenin, $C_{23}H_{32}O_6$, m.p. 251° (negative Legal test), is obtained from calotropin or its genin by heating with borax solution; it is hydrolysed by alkali to the corresponding acid, isocalotropic acid, $C_{23}H_{34}O_7$, m.p. 156° decomp. The action of hot normal NaOH eliminates the methyl-reductic acid and gives an isomeric genin, pseudo-calotropagenin, $C_{23}H_{32}O_6$, m.p. 241°, together with the corresponding acid which is formed by ring opening of the lactone, pseudo-calotropic acid, $C_{23}H_{34}O_7$, decomp. 228°.

III. Animal Cardiac Poisons of the Cholane Type: Toad Poisons

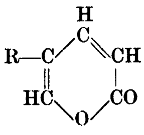
The poisonous substances which occur in the secretions from the glands of the skin of European and foreign species of toads, such as *Bufo vulgaris*, *B. japonicus*, *B. marinus* and *B. gargarizans*, are closely related to the vegetable cardiac poisons, and particularly to scillaren A. These compounds have long been used in eastern Asia in place of *Digitalis* preparations. The bufotoxins, as the poisonous substances are named, are compounds of the bufagins (also called bufagenins) with suberyl-arginine, which takes the place of the sugar component of the plant glycosides:



$$R{-}OOC{-}(CH_2)_6{-}CO{-}NH{-}\underset{\displaystyle COOH}{\underset{|}{CH}}{-}(CH_2)_3{-}NH{-}\underset{\displaystyle NH}{\underset{\|}{C}}{-}NH_2$$

R = bufagin residue

Complete hydrolysis of the original substance, therefore, gives the bufagin, suberic acid and arginine (*Wieland* and *Alles*, Ber. **55**, 1789). Most of the bufagins so far investigated contain 24 C-atoms, or are acetyl derivatives of such compounds, showing their close relationship to scillaren (above) on the one hand, and to the bile-acids on the other. Experimental proof of the presence of the cholane ring-system is given by the dehydrogenation of cinobufagin with Se (*Tschesche* and *Offe*, Ber. **68**, 1998; *Jensen*, Am. **57**, 2733); the typical hydrocarbon, $C_{18}H_{16}$, of *Diels* (3-methyl-cyclopenteno-phenanthrene) is obtained. The remaining five C-atoms form, as in scillaren-A, a lactonic side-chain. Since the products of acid hydrolysis of the toad poisons have the same absorption in the ultra-violet (maximum at 290–300 mμ) as scillaridin-A, it has been assumed that the same lactonic group



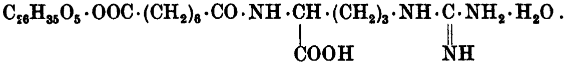
is present as in the squill glycosides (above) (*Wieland*, *Hesse* and *Hüttel*, Ann. **524**, 203; *Tschesche* and *Offe*, Ber. **69**, 2361). This conclusion has recently received support from the results of the ozonolysis of acetyl-bufotalin; Wieland and his collaborators (loc. cit.) identified formic and glyoxylic acids among the products. Moreover, the aldehyde group which would be expected as the result of the elimination of the aldo-enol group was shown to be present by the reduction of ammonical silver nitrate and the colour reaction with Schiff's reagent (*Wieland* and *Hesse*, Ann. **517**, 24; *Tschesche* and *Offe*, loc. cit.).

The remaining oxygen atoms in the molecules of the various toad poisons are present as secondary or tertiary hydroxyls, some of which are acetylated; one secondary OH is assumed by analogy to be on C_3; the positions of the other hydroxyls has not been established in all cases. Provisional formulae have been proposed by *Wieland*, *Hesse* and *Hüttel* (loc. cit.) and by *Tschesche* and *Offe* (loc. cit.)

The best-known poisons of this class are tabulated below:

Bufotoxin	Formula	M.p.	Bufagin (Bufogenin)	Formula	M.p.	⌐	Occurrence
Vulgaro-bufotoxin	$C_{40}H_{60}O_{10}N_4 \cdot H_2O$	205°	bufotalin	Acetyl deriv. of $C_{24}H_{34}O_5$	223° (dec.)		*Bufo vulgaris*
Gama-bufotoxin	$C_{38}H_{58}O_9N_4 \cdot H_2O$	210°	gamabufagin	$C_{24}H_{34}O_5$	255°	2	*Bufo japonicus*
Cino-bufotoxin	$C_{40}H_{58}O_{10}N_4$	200° (dec.)	cinobufagin	Acetyl deriv. of $C_{24}H_{32}O_5$	223°	3	*Bufo gargarizans*
Marino-bufotoxin	$C_{38}H_{56}O_9N_4 \cdot H_2O$	200° (dec.)	marinobufagin	$C_{24}H_{32}O_5$	213°	3?	*Bufo marinus*

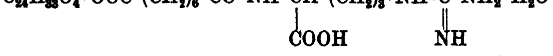
Vulgaro-bufotoxin (bufotoxin), $C_{40}H_{60}O_{10}N_4 \cdot H_2O$, m.p. 205° (dec.), the chief constituent of the skin-glands of the common toad, *Bufo vulgaris* (preparation: *Wieland, Hesse* and *Hüttel,* Ann. **524**, 210), is an ester of **bufotalin,** $C_{26}H_{36}O_6$, m.p. 223° decomp. and suberyl-arginine, $C_{16}H_{26}O_5N_4$ (*Wieland* and *Alles,* Ber. **55**, 1789):



$$C_{26}H_{35}O_5 \cdot OOC \cdot (CH_2)_6 \cdot CO \cdot NH \cdot \underset{\displaystyle COOH}{\underset{|}{CH}} \cdot (CH_2)_3 \cdot NH \cdot \underset{\displaystyle NH}{\underset{\|}{C}} \cdot NH_2 \cdot H_2O\,.$$

It is decomposed by total acid hydrolysis into bufotalien, $C_{24}H_{30}O_3$, m.p. 225° (bufotalan, $C_{24}H_{38}O_3$, has m.p. 199°), acetic acid, suberic acid, m.p. 140°, and arginine, $C_6H_{14}O_2N_4$ (picrolonate m.p. 230°). The conversion of bufotoxin, with two double bonds, into bufotalin seems to take place only in the animal organism; acid hydrolysis always eliminates one mol. of acetic acid and one of water, and gives bufotalien with four double bonds. Dehydrogenation of bufotalien with Se yields small amounts of chrysene, formed by ring-enlargement from 3-methyl-cyclopentenophenanthrene (*Wieland* and *Hesse,* Ann. **517**, 25). By reduction of acetyl-bufotalien, $C_{26}H_{32}O_4$, m.p. 184°, via acetoxy-cholanic acid, $C_{26}H_{42}O_4$, into iso-bufo-cholanic acid, $C_{24}H_{40}O_2$, m.p. 179°, a reaction analogous to the conversion of anhydro-scillaridin-A into allo-cholanic acid, *Wieland, Hesse* and *Meyer* (Ann. **498**, 272) were able to bridge the gap to an acid of the cholane series; the acid obtained, however, is not identical with any of the cholanic acids so far known. The presence of a secondary alcohol group in bufotalin is shown by its oxidation with CrO_3 to bufotalone, $C_{26}H_{34}O_6$, m.p. 265^c (oxime m.p. 226°). It is worth noting that this ketone is converted by dilute alcoholic alkalis into the isomeric anhydro-bufotalonic acid, $C_{26}H_{34}O_6$, m.p. 233° decomp., a reaction probably analogous to the formation of the iso-compounds in the *Digitalis* and *Strophanthus* glycosides (*Wieland* and *Hesse,* Ann. **517**, 25). By-products isolated from the secretion of *Bufo vulgaris* are: bufotalidin, $C_{24}H_{32}O_6$, m.p. 228° (acetyl compound m.p. 245°), which is an unsaturated lactone with three double bonds, and bufotalinin, of unknown formula.

While bufotoxin, the poisonous substance of the European toad, is a mono-acetyl choladienic acid lactone, the poisonous compound from the skin of the Japanese toad (*Bufo japonicus*), **gamabufotoxin,** $C_{38}H_{58}O_9N_4 \cdot H_2O$, m.p. 210°:



$$C_{24}H_{33}O_4 \cdot OOC \cdot (CH_2)_6 \cdot CO \cdot NH \cdot \underset{\displaystyle COOH}{\underset{|}{CH}} \cdot (CH_2)_3 \cdot NH \cdot \underset{\displaystyle NH}{\underset{\|}{C}} \cdot NH_2 \cdot H_2O$$

is derived from an acetyl-free lactone. Removal of the suberyl-arginine gives **gamabufagin** (gamabufogenin), $C_{24}H_{34}O_5$, m.p. 255° (diacetyl deriv. m.p. 252°), which can be isolated in small quantities from the skin extracts. Acid hydrolysis of the poison, however, only gives anhydro-gamabufagin, $C_{24}H_{32}O_4$, m.p. 260°. Extraction of the skin of Japanese toads also gives gamabufotalin, $C_{27}H_{38}O_6$, m.p. 263° (diacetyl deriv. m.p. 225°) (*Kotake,* Ann. **465**, 12). An important feature of this by-product is that on catalytic hydrogenation or on warming with alcoholic potash the residue C_3H_5O, which is attached through an ether link, is eliminated; in the former case a dihydrocompound, $C_{24}H_{38}O_5 \cdot C_2H_5OH$, m.p. 133°, is formed, while in the latter the lactone ring is also opened to form gamabufotalinic acid, $C_{24}H_{36}O_6$, m.p. 209°. Anhydro-gamabufotalin, $C_{27}H_{36}O_5$, m.p. 263°, is prepared by the action of conc. HCl upon gamabufotalin (*Kotake*, Ann. **466**, 11).

The Chinese drug *senso* or *ch'an su*, obtained from the parotid secretion of the Chinese toad (*Bufo gargarizans*), contains **cinobufotoxin**, $C_{40}H_{58}O_{10}N_4$, m.p. 200° decomp. (*Jensen* and *Chen*, J. Biol. Chem. **87**, (1930) 741). Elimination of suberic acid and arginine leaves the unsaturated **cinobufagin**, $C_{26}H_{34}O_6$, m.p. 223° (3 ⌈) (preparation: *Tschesche* and *Offe*, Ber. **69**, 1998): mono-acetyl deriv. m.p. 202°. The molecular weight of the compound has been confirmed by X-ray crystal analysis (*Crowfoot* and *Jensen*, Am. **58**, 2018). The acetyl derivative takes up three mol. of H_2 by catalytic reduction to give α- and β-hexahydro-cinobufagin-mono-acetate, $C_{28}H_{42}O_7$, α- m.p. 238°, β- m.p. 250° decomp. Like bufotalin, cinobufagin contains one acetyl group. One secondary OH can be identified by oxidation with chromic mixture, which gives cinobufagone, $C_{26}H_{32}O_6$, m.p. 238° (*Tschesche* and *Offe*, Ber. **69**, 2361). By heating cinobufagin with Se at 270–320°, Tschesche and Offe obtained Diels' hydrocarbon, 3-methyl-cyclopentenophenanthrene.

For pseudo-bufotalin from "*senso*", see *Kondo* and *Ikawa*, J. pharm. Soc. Japan **53** (1933), 2, 62; **55** (1935), 49, 144.

The secretion of the Jamaica toad, *Bufo marinus*, yields marino-bufagin, $C_{24}H_{32}O_5$, m.p. 213°, formed from the corresponding suberyl-arginine compound, marino-bufotoxin, $C_{38}H_{56}O_9N_4 \cdot H_2O$, m.p. 200° (*Chen* and *Chen*, J. Pharm. Exp. Ther. **49** (1933), 514).

VI. STEROLS, BILE ACIDS AND SCYMNOL[1]

The two former classes of substance have been dealt with briefly in vol. I, pp. 753 to 755, but since the publication of that volume, considerable advances have been made in our knowledge of the group, and the formulae given there have been superseded; the constitutions of the sterols and bile acids can now be regarded as established beyond doubt, and the large amount of evidence upon which their present formulation is based is summarised in this chapter.

The sterols and bile acids have the same tetracyclic carbon skeleton as the toad poisons considered above, and as many of the saponins. The occurrence of sterols as normal constituents of cellular fats, the cooperation of the bile acids in the digestion of fats, and the relationships which both classes of compounds show to other physiologically important compounds such as the sex hormones, illustrate the importance of the two classes of compounds.

The most important natural sterols are tabulated below, together with their characteristic derivatives; the bile acids are then treated similarly. Finally both classes are considered together in a discussion of the important experimental work that has led to the constitutions assigned to these compounds today.

STEROLS

The sterols together with the phosphatides are the most important compounds that accompany animal and vegetable fats and oils.

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[1] *L. F. Fieser*, The Chemistry of Natural Products related to Phenanthrene. Am. Chem. Soc. Monographs, 1937. — *H. Lettré* and *H. H. Imhoffen*, Über Sterine und Gallensäuren und verwandte Naturstoffe. Stuttgart, 1936.

There they are found partly free, partly esterified with the higher fatty acids, and in the plant kingdom they occur also as glycosides (sterolins, p. 364). It is, however, remarkable that only small quantities of sterols can be isolated from the fats of pathogenic bacteria (e.g. tubercle and diphtheria bacilli) (*Anderson, Schoenheimer, Crowder* and *Stodola*, Z. physiol. Chem. **237**, 40; *Sifferd* and *Anderson*, ibid. **239**, 270), and in these fats the phosphatides also vary from the normal in composition. Brain and nerve tissue and yolk of egg are very rich in cholesterol, and human gall-stones consist chiefly of cholesterol. To isolate the sterols, the fat is hydrolysed with alcoholic alkali, and the sterol extracted with ether or light petroleum. Several sterols are usually present in any starting material, and the separation of these is very tedious on account of their similarities in solubility and the formation of molecular compounds. The preparation of the pure substance is best carried out by fractional crystallisation of the acetyl compound, or via the bromo-derivative (*Windaus* and *Hauth*, Ber. **39**, 4378).

The sterols are well-crystalline substances which contain a secondary alcohol group in a hydroaromatic ring, and have all the properties of such a compound; e.g. they form esters and urethanes, and in oxidation they give cyclic ketones and by ring-fission dicarboxylic acids. All sterols isolated from natural fats are characterised by their ability to form more or less sparingly soluble addition compounds with an alcoholic solution of digitonin, the so-called "digitonides"; these normally contain 1 mol. of sterol to 1 mol. of digitonin ($C_{55}H_{90}O_{29}$), and can be used, not merely for qualitative, but also for quantitative analysis (*Windaus*, Ber. **42**, 238; *Schönheimer* and *Dam*, Z. physiol. Chem. **215**, 59), and for the purification of the sterols (*Windaus*, ibid. **65**, 110). The presence of the free sterol and a certain spatial configuration of the secondary alcohol group are conditions for the formation of these sparingly soluble compounds. Hence sterol esters and certain sterols prepared artificially are not precipitated by digitonin. This reaction explains the fact, which has been long known, that cholesterol increases the haemolytic effect of digitonin and other saponins on the red blood corpuscles.

When conc. H_2SO_4 is poured beneath a chloroform solution of a sterol, a more or less intense colour appears (Salkowski's reaction); this also occurs in the presence of acetic anhydride (Liebermann-

Sterol	Formula	$\vert^{=}$	M.p.	$[\alpha]_D$
Cholesterol	$C_{27}H_{46}O$	1	149°	— 38·8°
Coprosterol	$C_{27}H_{48}O$	0	102°	+ 23·5°
Ostreasterol	$C_{29}H_{48}O$	2	142°	— 43·9°
Lanosterol	$C_{30}H_{50}O$	2	141°	+ 58°
Agnosterol	$C_{30}H_{48}O$	3	162°	+ 70·6°
Ergosterol	$C_{28}H_{44}O$	3	163°	— 133°
Sitosterol..	$C_{29}H_{50}O$	1	138°	— 33·9°
Stigmasterol	$C_{29}H_{48}O$	2	170°	— 45°
Zymosterol	$C_{27}H_{44}O$	2	110°	+ 52·2°

Burchard reaction). Antimony trichloride and trichloracetic acid in $CHCl_3$ solution also cause colourations, which vary from sterol to sterol, but depend chiefly upon the position and number of double bonds in the molecule. These colour reactions are not specific for sterols, and are given to some extent by many bile acids and other compounds.

The sterols are colourless substances, which have a characteristic absorption spectrum only in the ultra-violet; this is displaced towards the shorter or longer wave-lengths according to the number of double bonds in the molecule.

The table below shows the most important natural animal and vegetable sterols, and their characteristic derivatives.

It is noteworthy that ostreasterol can be converted into dihydro-sitosterol (sitostanol) by the addition of four hydrogen atoms; this is a transition from a sterol of animal origin to one of plant origin (*Bergmann*, J. Biol. Chem. **104** (1934), 317, 553). Lanosterol, $C_{30}H_{50}O$, and agnosterol, $C_{30}H_{48}O$, were formerly classed with the sterols; they are not, however, cholane derivatives, but members of the triterpenoid group (*Schulz*, Z. physiol. Chem. **238**, 35).

BILE ACIDS

The investigation of the contents of the bile of mammals, birds and fishes led to the discovery of the bile acids, which are physiologically active in several ways. In constitution they are closely related to cholesterol, a fact of great scientific interest.

They have an important function in fat resorption, which is based upon the formation of water-soluble molecular compounds with the free fatty acids ("cholic acid principle", see *Heinrich* and *Sorge*, Z. physiol. Chem. **97**, 1; *Pohl*, Z. exp. Med. **30** (1922), 423), and in the resorption of provitamin A (carotene, see *v. Euler* and *Klussmann*, ibid. **219**, 215); further they activate the digestive enzymes (intestinal lipase, see *Kaziro* and *Tsuji*, J. Biochem. **11** (1930), 333; cf. the enzymatic synthesis of cholesterol esters, *Nedswedski*, Z. physiol. Chem. **236**, 69; **239**, 165; nuclease, see *Okamura*, Arb. med. Univ. Okayama **2** (1930), 245), and show saponin-like properties in their control of the hydrogen ion concentration in digestion. They have haemolytic properties (see *Donnelly* and *Michell*, Amer. J. Physiol. **79**, 297; *Sen* and *Basu*, J. Indian Chem. Soc. **5** (1928), 1; limiting

Acetate		Benzoate		Occurrence
M.p.	$[\alpha]_D$	M.p.	$[\alpha]_D$	
114°	— 47·4°	148 or 179°	—	Constituent of all animal cells
85°	—	115°	—	Faeces
134°	— 45·8°	152°		*Lamellibranchiae* (oysters, clams)
114°	+ 56·2°	191·5°	+ 74·5°	Wool fat
174°	+ 90·2°	203°	+ 103·6°	Wool fat
181°	— 90°	168°	— 68°	Yeast, fungi, ergot
128°	— 38·5°	145·5°	—	Chief sterol of the fats of higher plants
141°	— 55°	160°	—	Calabar beans, carrots, soya beans
106°	+ 33·5°	124 or 138°	+ 36·4°	Yeast

conc. for bufo-desoxycholic acid 1:3,200, for desoxycholic acid 1:3,000, for apocholic acid 1:1,500, for cholic acid 1:750, see *Okamura*, J. Biochem. **8** (1927), 351; *Kaziro* and *Tsuji*, ibid. **11** (1930), 333) which is shown by their effect on the beating of the heart (*Wieland* and *Hildenbrand*, Arch. exp. Path. **85** (1919), 199; *Wieland*, ibid. **86** (1920), 92; *Tappolet*, C. 1924 I 1411; *Takahashi*, C. 1927 II 599; "cadechol", composed of desoxycholic acid and camphor, see p. 282, is used pharmaceutically), and by their bactericidal properties (*Kozlowski*, J. Exp. Med. **42** (1925), 453; *Neufeld* and *Etinger-Tulczynska*, C. 1930 I 1483; for the lysis of pneumococci, see *Downie*, *Stent* and *White*, Brit. J. Exp. Path. **12** (1931), 1; *Ziegler*, J. Lab. Clin. Med. **17** (1932), 317).

The following table summarises the bile acids so far isolated:

Bile acid[1]	Formula	M.p.
Lithocholic acid (3-hydroxy-cholanic acid)	$C_{24}H_{40}O_3$	186°
Desoxycholic acid (3:12-dihydroxy-cholanic acid)	$C_{24}H_{40}O_4$	172°
Cholic acid (3:7:12-trihydroxy-cholanic acid) ..	$C_{24}H_{40}O_5$	195°
3-Hydroxy-12-keto-cholanic acid	$C_{24}H_{38}O_4$	155–160°
Sterocholic acid	$C_{28}H_{46}O_4$	252°
Cheno- or anthropo-desoxycholic acid (3:7-dihydroxy-cholanic acid)	$C_{24}H_{40}O_4$	140°
Hyo-desoxycholic acid (3:6-dihydroxy-cholanic acid)	$C_{24}H_{40}O_4$	197°
Urso-desoxycholic acid	$C_{24}H_{40}O_4$	—
Bufo-desoxycholic acid	$C_{24}H_{40}O_4$	—
Nutriacholic acid	$C_{24}H_{40}O_5$	198°

In the organism the bile acids are usually conjugated with glycocoll or taurine alone, e.g. as glycocholic acid, $C_{23}H_{39}O_3$ CO NH CH_2 COOH, m.p. 130°; taurocholic acid, $C_{23}H_{39}O_3 \cdot CO\ NH \cdot CH_2 \cdot CH_2 \cdot SO_3H$, or together with fatty acids as glyco- or tauro-choleic acids (*Hammarsten*, Z. physiol. Chem. **43**, 127; *Wieland*, ibid. **106**, 181; *Tanaka*, ibid. **220**, 39; *Kazuno* and *Yamazaki*, ibid. **224**, 160).

The varying oxygen content of the acids arises from differences in the number of hydroxyl groups present; this is shown by the preparation of derivatives (e.g. acetyl compounds), and by their dehydration and reduction to the saturated cholanic acid, $C_{24}H_{40}O_2$. Lithocholic, desoxycholic, cheno-desoxycholic, hyo-desoxycholic and cholic acids all give the same cholanic acid, m.p. 164°; urso-desoxycholic and bufo-desoxycholic acids give isomeric acids, m.ps. 153° and 236°. The position of the hydroxyl groups in the molecule is established by oxidation (cf. *Schenk*, ibid. **87**, 71; *Borsche*, Ber. **52**, 1353), and, taking advantage of the fact that the reactivity of a hydroxyl depends on its position, by interconversion of the hydroxy-acids (cholic acid → anthropo-desoxycholic acid, see *Kawai*, Z. physiol. Chem. **214**, 71; desoxycholic acid → lithocholic acid, see *Wieland*, *Dane* and *Scholz*, ibid. **211**, 266) (cf. also *Wieland* and *Dane*, ibid. **212**, 41; *Wieland* and *Kapitel*, ibid. 269; *Wieland*, *Dane* and *Martius*, ibid. **215**, 15); the structures in column I of the above table have been determined in this way.

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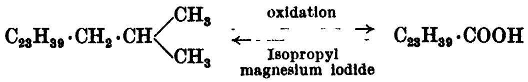
[1] For the numbering, see formula, p. 553.

THE CONSTITUTION OF THE STEROLS AND BILE ACIDS[1]

1. General considerations. — The double bond of cholesterol, which is in ring B, $\beta\gamma$- to the OH-group (for a summary of the evidence see *Windaus*, ibid. **213**, 148–154), can be reduced catalytically to dihydro-cholesterol (β-cholestanol), m.p. 142°, $[\alpha]_D + 28{\cdot}8^0$ (ether) (acetyl-compound m.p. 111°); replacement of the OH of the latter by H gives the fundamental tetracyclic hydrocarbon, cholestane, $C_{27}H_{48}$, m.p. 80°. Other natural sterols can likewise be converted into their fundamental saturated hydrocarbons. On the other hand, most natural bile acids are derived from the hydroxyl-free acid, cholanic acid, $C_{24}H_{40}O_2$, m.p. 164° (p. 556).

Occurrence	Literature
Ox bile	Z. physiol. Ch. **73**, 234; **110**, 123
Ox bile	Z. physiol. Ch. **97**, 1; **98**, 59
Ox bile	Z. physiol. Ch. **80**, 297; **106**, 193
Ox bile	Z. physiol. Ch. **214**, 47
Ox bile	Z. physiol. Ch. **214**, 57
Ox, goose and human bile	Z. physiol. Ch. **140**, 167, 186; **148**, 225; **157**, 180; **214**, 71
Pig and hippopotamus bile	Ann. **433**, 282; **447**, 233; Ber. **52**, 1918
Bear bile	J. Biochem. 7 (1921), 505; Z. physiol. Ch. **185**, 151; **197**, 206
Toad bile	J. Biochem. 8 (1928), 351; **10** (1929), 5; **11** (1929), 103
Beaver bile	Z. physiol. Ch. **220**, 106

Cholanic acid has three carbon atoms less than cholestane, and the relationship which had often been postulated between them was established experimentally by *Windaus* (Z. physiol. Chem. **100**, 167): he converted cholestane into allo-cholanic acid, and pseudo-cholestane into cholanic acid (*Windaus* and *Neukirchen*, Ber. **52**, 1915), by oxidation with CrO_3, acetone being eliminated:



$$C_{23}H_{39}\cdot CH_2\cdot CH\begin{matrix}CH_3\\ CH_3\end{matrix}\ \underset{\text{Isopropyl magnesium iodide}}{\overset{\text{oxidation}}{\rightleftarrows}}\ C_{23}H_{39}\cdot COOH$$

This important relationship was later confirmed by the reverse procedure, the synthesis of pseudo-cholestane from cholanic ester and isopropyl magnesium iodide (*Wieland* and *Jacobi*, Ber. **59**, 2064).

For a long time it was uncertain whether the HO-group in cholesterol was on the same C-atom as the HO-group in lithocholic acid. This question was answered in the affirmative by the isolation of identical or stereoisomeric acids (*Wieland* and *Dane*, Z. physiol.

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[1] Useful reviews: *Windaus*, Ann. Rev. Biochem. **1** (1932), 109: *Rosenheim* and *King*, ibid. **8** (1932), 87: *Sobotka*, Chem. Rev. **15** (1934), 311.

Chem. **212**, 41) in the oxidative degradation of the carbon skeleton (see p. 553). The results obtained mainly by Windaus and his school with cholesterol, and by Wieland and his school with the bile acids, indicated that both classes of compounds have the same carbon skeleton.

2. Side-chains. — The isopropyl group eliminated in the oxidation of cholestane to allocholanic acid (see above) is only a part of a longer aliphatic side-chain. The nature of the whole side-chain was disclosed chiefly by the oxidation of large quantities of cholesterol with CrO_3, which gave methyl-isohexyl-ketone (*Windaus* and *Resau*, Ber. **46**, 1246), and by the oxidation of cholic acid with HNO_3, which yielded, among other products, α-methyl-glutaric acid, m.p. 77°. The structures of the side chains

$R\cdot CH(CH_3)\cdot CH_2\cdot CH_2\cdot CH_2\cdot CH(CH_3)_2$ in cholesterol
$R\cdot CH(CH_3)\cdot CH_2\cdot CH_2\cdot COOH$ in the bile acids

are thereby established experimentally, and have been confirmed by the successive degradation of the side chain of cholanic ester (*Wieland*, *Schlichting* and *Jacobi*, Z. physiol. Chem. **161**, 80).

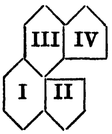
The side chain is not, however, the same in all sterols. Sometimes it is unsaturated, and in sterols with more than 27 C-atoms in the molecule (cf. table, p. 550) the extra C-atoms form further branches in the side chain (*Reindel* and *Kipphan*, Ann. **493**, 181; *Guiteras*, *Nakamiya* and *Inhoffen*, Ann. **494**, 116; *Guiteras*, Z. physiol. Chem. **214**, 89):

e.g. Ergosterol $C_{28}H_{44}O$: $R\cdot CH(CH_3)\cdot CH{=}CH\cdot CH(CH_3)\cdot CH(CH_3)_2$
Stigmasterol $C_{29}H_{48}O$: $R\cdot CH(CH_3)\cdot CH{=}CH\cdot CH(C_2H_5)\cdot CH(CH_3)_2$.

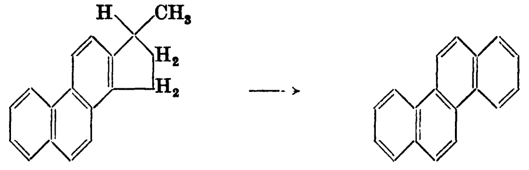
Finally, the sterols and bile acids contain two methyl groups attached to tertiary carbon atoms; the position of these will be dealt with after the discussion of the fundamental carbon skeleton.

3. The tetracyclic ring-system. — The determination of the structure of the fundamental ring-system, which, according to the empirical formula for cholestane, contains four hydroaromatic rings, was much more difficult.

Systematic application of the method of oxidative fission of the rings one by one established the positions of the hydroxyl groups and of any double bonds present, and the size of ring broken could be discovered by using *Blanc's* rule. According to this (C. r. **144**, 1356), when a dicarboxylic acid is heated with acetic anhydride, or its Ca salt distilled, an anhydride is obtained if the carboxyl groups are in the 1·3, 1·4 or 1·5 positions, and a ketone if they are 1·6 or greater. The results of more recent investigations have shown, however, that with complex dicarboxylic acids, Blanc's rule may fail, and the use of it led to errors in the determination of the size of one of the rings (*Wieland* and *Dane*, Z. physiol. Chem. **210**, 275). For this reason, the ring-system below originally suggested has not been confirmed by later work (see *Wieland*, Ber. **67** (A), 27–39).



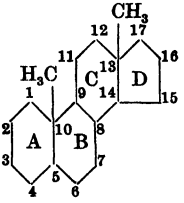
The dehydrogenation of cholesterol and the bile acids by Diels' method with selenium or with palladium, taken in conjunction with the oxidation results, finally established the ring-system present, and showed the above formula to be incorrect. Dehydrogenation gave as chief products two hydrocarbons, chrysene, $C_{18}H_{12}$, and its precursor, the hydrocarbon $C_{18}H_{16}$, 3-methyl-cyclopentenophenanthrene (*Diels*, *Gädke* and *Körding*, Ann. **459**, 1; *Diels* and *Karstens*, Ann. **478**, 129; *Diels* and *Gädke*, Ber. **58**, 1231; **60**, 140; *Ruzicka*, *Goldberg* and *Thomann*, Helv. **16**, 812; synthesis: *Harper*, *Kon* and *Ruzicka*, J. **1934**, 124; *Hillemann*, Ber. **68**, 102). The transformation of the latter into chrysene is analogous to other pyrogenic ring-enlargements which are known (*Raudnitz*, *Petrů* and *Stadler*, Ber. **66**, 879; *Linstead*, "Dehydrogenation", Ann. Rep. Chem. Soc. **33** (1936), 294).



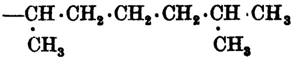
Diels' hydrocarbon $C_{18}H_{16}$ Chrysene

The determination of the size of the elementary cell in sterol crystals by the X-ray method (*Bernal*, Chem. and Ind. **51** (1932), 466; Nature **129** (1932), 277) was also important evidence. The results were quite incompatible with the old formula, using the known atomic distances, but in good agreement with the new formula.

As the result of these new chemical and physico-chemical investigations, the fundamental tetracyclic skeleton of these compounds can be given the following formula (*Rosenheim* and *King*, Chem. and Ind. **51** (1932), 954; *Wieland* and *Dane*, Z. physiol. Chem. **210**, 274):

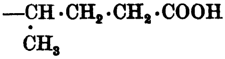


On C-atom 17
in cholesterol derivatives:



$$-\underset{CH_3}{CH}\cdot CH_2\cdot CH_2\cdot CH_2\cdot \underset{CH_3}{CH}\cdot CH_3$$

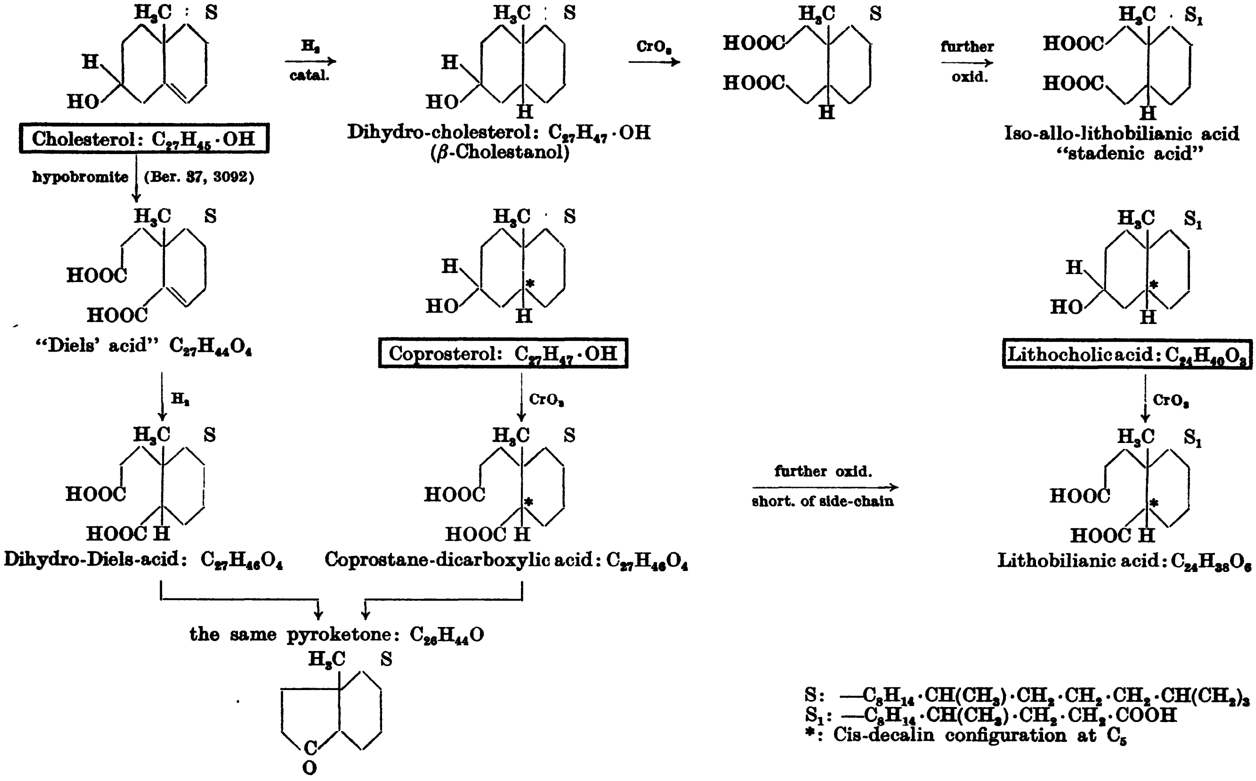
in bile acids:



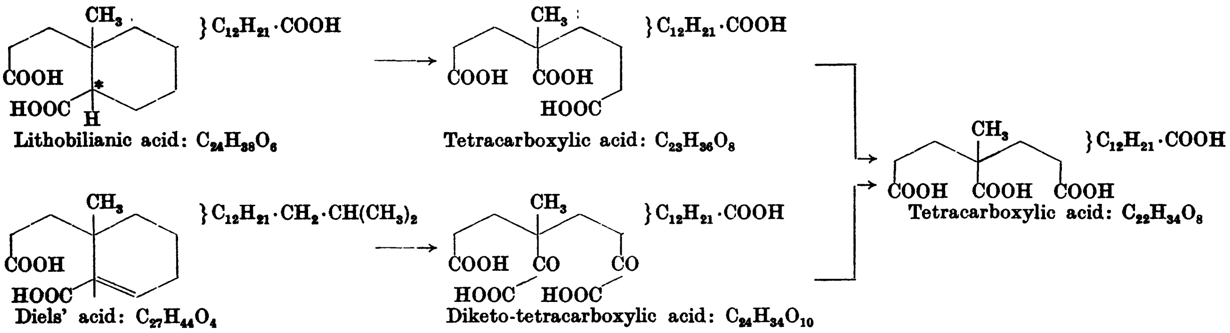
$$-\underset{CH_3}{CH}\cdot CH_2\cdot CH_2\cdot COOH$$

The *oxidative degradation of the tetracyclic ring-system*.—Of the enormous amount of experimental work, only that essential for the determination of the ring-system is mentioned here.

a) Ring A. The following degradations of cholesterol, coprosterol and lithocholic acid show the relationships in the 6-ring A. In cholesterol, coprosterol and the bile acids, this ring carries a hydroxyl in position 3, and it is important to note that the bond which is broken to open the ring on oxidation is determined by the spatial configuration about the C_5-atom (*Wieland*, *Dane* and *Martius*, Z. physiol. Chem. **215**, 18). In coprosterol and lithocholic acid, which


Cholesterol: $C_{27}H_{45}\cdot OH$
H_2 catal.
Dihydro-cholesterol: $C_{27}H_{47}\cdot OH$ (β-Cholestanol)
CrO_3
further oxid.
Iso-allo-lithobilianic acid "stadenic acid"
hypobromite (Ber. 37, 3092)
"Diels' acid" $C_{27}H_{44}O_4$
Coprosterol: $C_{27}H_{47}\cdot OH$
Lithocholic acid: $C_{24}H_{40}O_3$
H_2
CrO_3
CrO_3
further oxid. short. of side-chain
Dihydro-Diels-acid: $C_{27}H_{46}O_4$
Coprostane-dicarboxylic acid: $C_{27}H_{46}O_4$
Lithobilianic acid: $C_{24}H_{38}O_6$
the same pyroketone: $C_{26}H_{44}O$

S: —$C_8H_{14}\cdot CH(CH_3)\cdot CH_2\cdot CH_2\cdot CH_2\cdot CH(CH_3)_2$
S₁: —$C_8H_{14}\cdot CH(CH_3)\cdot CH_2\cdot CH_2\cdot COOH$
*: Cis-decalin configuration at C_5



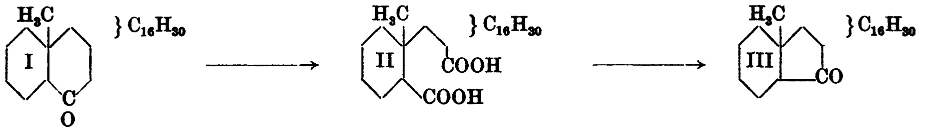
Lithobilianic acid: $C_{24}H_{38}O_6$

Diels' acid: $C_{27}H_{44}O_4$

Tetracarboxylic acid: $C_{23}H_{36}O_8$

Diketo-tetracarboxylic acid: $C_{24}H_{34}O_{10}$

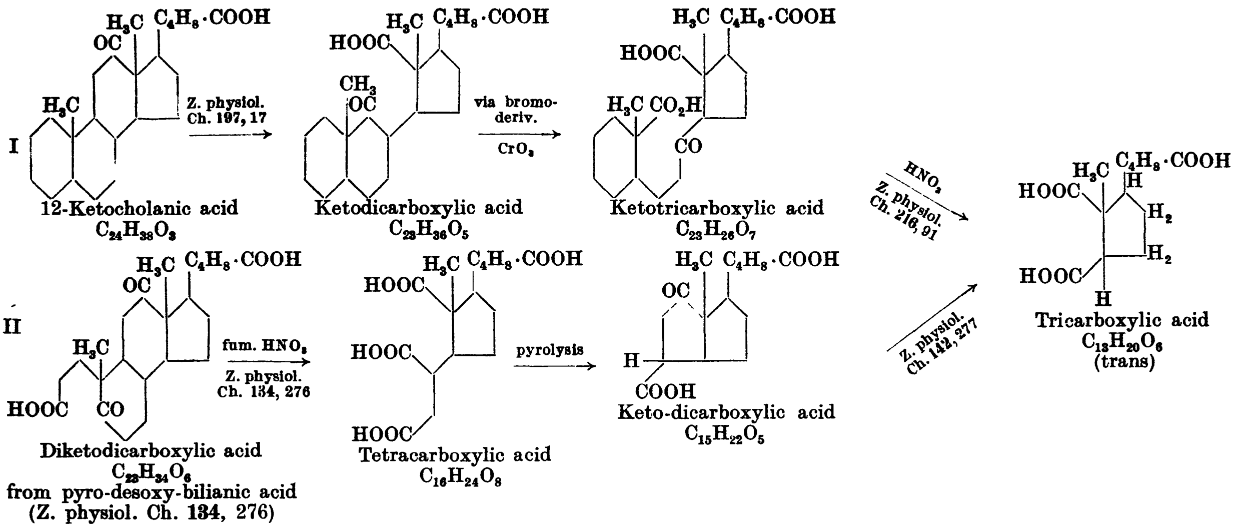
Tetracarboxylic acid: $C_{22}H_{34}O_8$

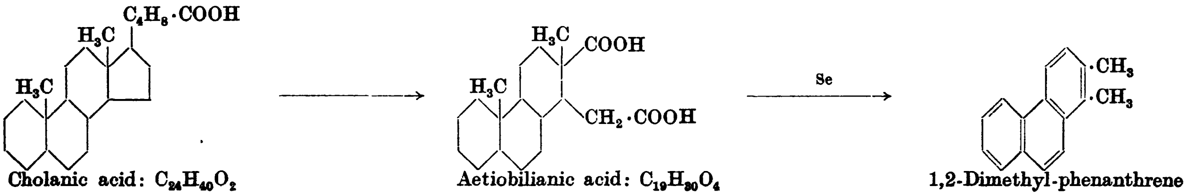


Cholestan-6-one

Dicarboxylic acid: $C_{27}H_{46}O_4$

Pyroketone: $C_{26}H_{44}O$.


I
II
H_3C
OC
$C_4H_8\cdot COOH$
Z. physiol. Ch. 197, 17
12-Ketocholanic acid
$C_{24}H_{38}O_3$
$HOOC$
CH_3
Ketodicarboxylic acid
$C_{23}H_{36}O_5$
via bromo-deriv.
CrO_3
CO_2H
CO
Ketotricarboxylic acid
$C_{23}H_{26}O_7$
HNO_3
Z. physiol. Ch. 216, 91
Z. physiol. Ch. 142, 277
H_2
H
Tricarboxylic acid
$C_{13}H_{20}O_6$
(trans)
fum. HNO_3
Z. physiol. Ch. 134, 276
Diketodicarboxylic acid
$C_{23}H_{34}O_6$
from pyro-desoxy-bilianic acid
(Z. physiol. Ch. 134, 276)
pyrolysis
Tetracarboxylic acid
$C_{16}H_{24}O_8$
$COOH$
Keto-dicarboxylic acid
$C_{15}H_{22}O_5$


$C_4H_8\cdot COOH$
H_3C
Cholanic acid: $C_{24}H_{40}O_2$
$COOH$
$CH_2\cdot COOH$
Aetiobilianic acid: $C_{19}H_{30}O_4$
Se
$\cdot CH_3$
1,2-Dimethyl-phenanthrene

have the cis-decalin configuration at this C-atom (*Ruzicka, Furter* and *Thomann*, Helv. **16**, 327), ring opening takes place chiefly between C_3 and C_4; in reduced cholesterol derivatives and allo-cholanic acid derivatives, which have rings A and B condensed together in the trans position, it takes place between C_2 and C_3 (iso-acid series). The above formulae (p. 554) show the most important relationships of ring A; an important point to be noted is that coprosterol and lithocholic acid are degraded to the same dicarboxylic acid, lithobilianic acid (*Langer*, Z. physiol. Chem. **216**, 189).

The conversion of cholestanol and of hyo-desoxycholic acid into 3-hydroxy-allo-cholanic acid (*Windaus* and *Hossfeld*, Z. physiol. Chem. **145**, 177; *Wieland* and *Dane*, ibid. **212**, 41) is a further argument in favour of the conclusion that the hydroxyl group in ring A occupies the same position both in the sterols and the bile acids.

b) Penetration from ring A into ring B. Further oxidation of lithobilianic acid (mentioned above), and of the so-called "Diels' acid", can lead to the opening of ring B which is attached to ring A. It is important to note that here, too, both acids give the same final degradation product (*Windaus*, Ber. **42**, 3770; *Wieland* and *Kulenkampff*, Z. physiol. Chem. **108**, 295; *Wieland* and *Schulenburg*, ibid. **114**, 167; *Wieland, Dane* and *Scholz*, ibid. **211**, 261); cf. formulae on p. 554.

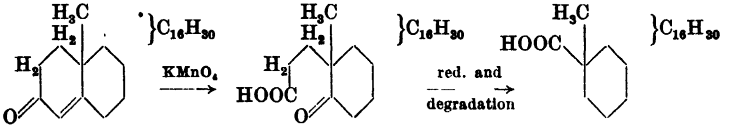
c) The size of ring B is shown most clearly by the behaviour of the dicarboxylic acid (II), $C_{27}H_{46}O_4$, obtained by oxidation of cholestane-6-one (I). Thermal decomposition of its Ba salt yields a pyro-ketone, $C_{26}H_{44}O$ (III) (*Stange*, ibid. **218**, 74; cf. formulae, p. 555).

d) Ring C. This 6-ring can only be attacked by oxidation by starting with the bile acids, and in particular with desoxycholic acid. Further degradation of the acid obtained leads finally by various routes to cyclopentane-carboxylic acids, which are derivatives of ring D. Two such ways are shown on page 556: (I) from 12-keto-cholanic acid (*Wieland* and *Posternak*, ibid. **197**, 17), and (II) from desoxycholic acid, via desoxybilianic acid (*Wieland* and *Schlichting*, ibid. **134**, 276; *Wieland* and *Dane*, ibid. **216**, 93).

e) Ring D. This last ring can only be opened by oxidation by progressive degradation of the side-chain (*Wieland, Schlichting*, and *Jacobi*, ibid. **161**, 80). This leads to aetiobilianic acid, which is pyrolysed to an anhydride. Ring D thus behaves as a 5-ring, in agreement with the results given under d). It should be noted that aetiobilianic acid is dehydrogenated by Se to the known 1:2-dimethylphenanthrene (*Butenandt, Weidlich* and *Thompson*, Ber. **66**, 601), which proves that rings A, B and C form a phenanthrene ring-system (see formulae, p. 556).

The following observations indicate the steric configuration of the rings. The behaviour on pyrolysis of the dicarboxylic acids obtained by the fission of ring A between C_{2-3} and C_{3-4} (*Windaus*, Ann. **447**, 233), and the comparison of the physical constants (density, molecular refraction, m.p.) with those of decalin-derivatives (*Ruzicka, Furter* and *Thomann*, Helv. **16**, 327), shows that rings A and B are cis in cholanic acid and coprosterol. In a similar way, it is shown that in cholestane the two rings are condensed in the trans arrangement (*Lettré*, Z. physiol. Chem. **221**, 73). From the X-ray results, rings B and C are in the trans position (*Ruzicka*, *Furter* and *Thomann*, loc. cit.). The trans configuration of the tricarboxylic acid $C_{13}H_{20}O_6$ (see above), obtained by the degradation of desoxycholic acid, indicates that rings C and D are in the trans position (*Wieland* and *Dane*, Z. physiol. Chem. 216, 91).

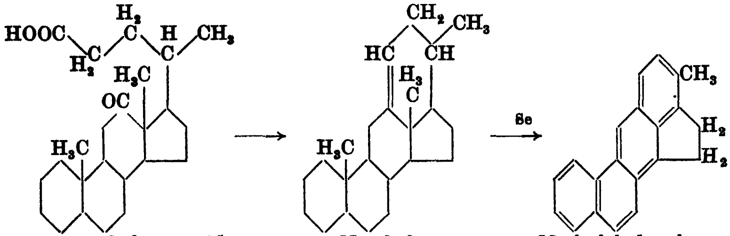
4. The position of the two methyl groups and of the side chain: Of the two quaternary methyl groups present in the sterols and bile acids, one was found to be next to the carboxyl group of the tricarboxylic acid, $C_{13}H_{20}O_6$, from desoxycholic acid (*Wieland* and *Dane*, loc. cit.) i.e. on C_{13} (sterol numbering); one of the methyl groups is eliminated as methane in the thermal decomposition of ergosterol-pinacol (cf. the formation of neo-ergosterol from ergosterol-pinacol, *Inhoffen*, Ann. 497, 130). A strict proof of the presence of a methyl group at C_{13} emerged also from work on the sex hormones (*Marker*, *Kamov*, *Oakwood* and *Laurius*, Am. 58, 1503). The position of the other methyl on C_{10} is determined by the tertiary character of the carboxyl group in the monocarboxylic acid, $C_{24}H_{42}O_2$, obtained from cholesterol by the following steps (*Tschesche*, Ann. 498, 185):



Cholestenone Keto-acid $C_{26}H_{44}O_3$ Acid $C_{24}H_{42}O_2$.

The formation of α-methylglutaric-α-carboxylic acid from the diketo-dicarboxylic acid, $C_{23}H_{34}O_6$ (cf. series II, p. 556), is also in favour of this view (*Wieland* and *Vocke*, Z. physiol. Chem. 177, 68). The degradation of the tricarboxylic acid, $C_{25}H_{42}O_6$, from cholesterol, to a tricarboxylic acid, $C_{23}H_{38}O_6$, which is a malonic acid, gives further support (*Windaus*, *Rosenbach* and *Riemann*, ibid. 130, 113).

Finally, the position of the side-chain remains to be determined. It is placed on C_{17} of the 5-ring because bile acids which have a carbonyl group at C_{12} can undergo intramolecular condensation in a kind of Perkin reaction (*Wieland*, ibid. 142, 191; *Wieland* and *Schlichting*, ibid. 150, 273; *Wieland* and *Wiedersheim*, ibid. 186, 229; *Borsche*, Ber. 47, 1435); e.g. 12-keto-cholanic acid, $C_{24}H_{38}O_3$, is converted into norcholene, $C_{23}H_{36}$:

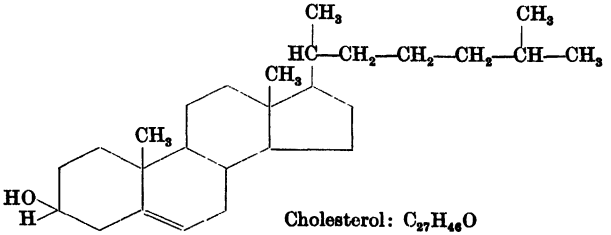


12-Ketocholanic acid Norcholene Methylcholanthrene

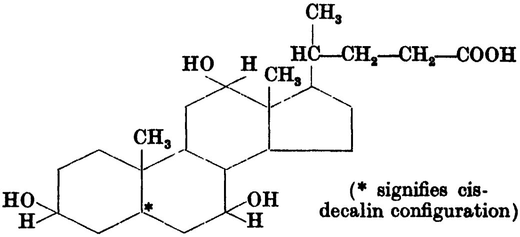
The dehydrogenation of norcholene with Se gives the yellow methylcholanthrene, $C_{21}H_{16}$, m.p. 174° (*Wieland* and *Dane*, Z. physiol. Chem. 219, 240), a strongly carcinogenic compound, the constitution of which has been proved by both degradation and synthesis (*Cook* and *Haslewood*, J. **1934**, 428; *Fieser* and *Seligman*, Am. **57**, 942).

Further evidence comes from the analogous cyclisation of pyrodesoxybilianic acid, $C_{23}H_{34}O_4$, to the unsaturated ketone, $C_{22}H_{32}O$ (*Shimizu* and *Kazuno*, Z. physiol. Chem. **224**, 155).

The results obtained from all this painstaking experimental work lead to the following formulae for cholesterol, the most important sterol, and cholic acid:



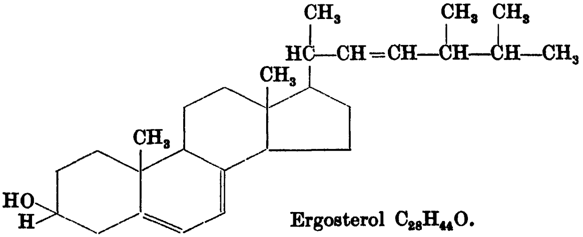
Cholesterol: $C_{27}H_{46}O$



(* signifies cis-decalin configuration)

Cholic acid $C_{24}H_{40}O_5$ [3: 7:12-trihydroxy-cholanic acid].

The other bile acids in the table on p. 550 have a similar structure. The constitution of ergosterol, the most important of the sterols with several double bonds, has been completely established: it is as follows (*Windaus*, *Inhoffen* and *v. Reichel*, Ann. **510**, 248; see *Cook*, Ann. Rep. Chem. Soc. **1936**, 346):

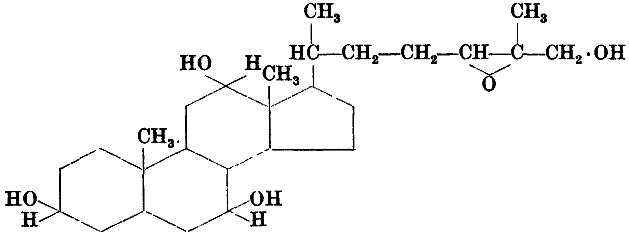


Ergosterol $C_{28}H_{44}O$.

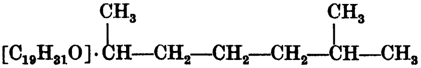
Interesting intermediates in the biological degradation of cholesterol to the bile acids are found in tetrahydroxy-bufostane and scymnol.

The winter bile of the toad *Bufo vulgaris japonicus* contains a tetrahydric sterol alcohol, **tetrahydroxy-bufostane,** $C_{27}H_{48}O_4$, m.p. 230° (tetracetate m.p. 55°). The function of the four oxygen atoms is shown by its oxidation with CrO_3 to a triketo-monocarboxylic acid, $C_{27}H_{40}O_5$, m.p. 222° (methyl ester trioxime m.p. 215°) (*Makino*, Z. physiol. Chem. **220**, 49).

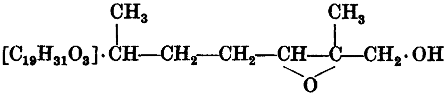
A sterol still richer in oxygen, **scymnol,** $C_{27}H_{46}O_5$, m.p. 187° (tetracetate m.p. 148°), occurs as a sulphuric ester in the bile of sharks. That it has a tetracyclic structure is proved by its reduction by HI to the hydrocarbon scymnane, $C_{27}H_{48}$. The CrO_3-oxidation to the triketo-monocarboxylic acid, $C_{27}H_{38}O_6$, m.p. 236° (trioxime decomp. 240–250°), shows that of the four hydroxyls of scymnol, three are present as secondary alcoholic, and one as a primary alcoholic group. The formation of a chlorhydrin proves that the fifth indifferent oxygen atom is present in an ethylene oxide ring, and the position of this is given by further oxidation of the above acid to the triketo-mono-carboxylic acid, $C_{24}H_{34}O_5$, m.p. 220° (methyl ester m.p. 233°), which is isomeric with dehydrocholic acid (3:7:12-triketocholanic acid). Since Clemmensen reduction gives 7:12-diketocholanic acid, m.p. 176° (methyl ester m.p. 135°), the position of two of the hydroxyl groups on the ring is established (*Windaus, Bergmann* and *König,* ibid. **189,** 148; *Tschesche,* ibid. **203,** 263); hence scymnol is given the following constitution:



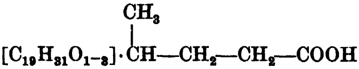
The sterols and bile acids are related to other important classes of compounds, such as the toad poisons, dealt with in the previous section, but more particularly with the physiologically important sex hormones (see p. 588), the saponins (p. 512) and the cardiac aglycones of the cholane group (see p. 525). The following formulae summarise these relationships:

Cholestanol 

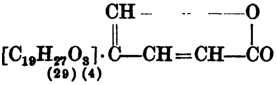
$$[C_{19}H_{31}O]\cdot\overset{CH_3}{\overset{|}{C}}H—CH_2—CH_2—CH_2—\overset{CH_3}{\overset{|}{C}}H—CH_3$$

Scymnol 

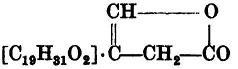
$$[C_{19}H_{31}O_3]\cdot\overset{CH_3}{\overset{|}{C}}H—CH_2—CH_2—\underbrace{CH—\overset{CH_3}{\overset{|}{C}}}_{O}—CH_2\cdot OH$$

Bile acids 

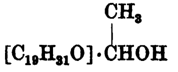
$$[C_{19}H_{31}O_{1-3}]\cdot\overset{CH_3}{\overset{|}{C}}H—CH_2—CH_2—COOH$$

Toad poisons 

$$[C_{19}H_{27}O_3]\cdot\underset{(29)\,(4)}{\overset{\overset{CH-\,-\,-O}{\|\qquad\quad|}}{C—CH=CH—CO}}$$

Digitoxigenin 

$$[C_{19}H_{31}O_2]\cdot\overset{\overset{CH———O}{\|\qquad\quad|}}{C—CH_2—CO}$$

Pregnanediol  (see Hormones)

$$[C_{19}H_{31}O]\cdot\overset{CH_3}{\overset{|}{C}}HOH$$

Sex hormones
male: $[C_{19}H_{30}O]$:O (see Hormones).
female: $[C_{18}H_{22}O]$:O (see Hormones)

The conversion of ergosterol, $C_{28}H_{44}O$, into the isomeric vitamin D_2 is discussed in the next section.

VII. VITAMINS[1]

The vitamins (so called by *Funk* in 1912) are constituents of human and animal foods, which in minute quantities are decisive for the maintenance of metabolism equilibrium, and hence for the preservation of health. On account of the small quantities present they are of no significance as suppliers of energy, but they are very important as organic catalysts in the degradations and changes which take place in the organic substances and minerals absorbed in the food. With the exception of a few animals which are able to build up this or that vitamin in their own organism, the vitamins are formed exclusively by the higher and lower plants (fungi, bacteria). A few vitamins are produced by the plant as an inactive precursor, the provitamin, which can then be converted into the active vitamin in the animal or human organism, either by a simple change, e.g. carotene → vitamin A, or by irradiation, as with ultra-violet light, ergosterol → vitamin D_2.

Certain diseases have long been known, the origin of which appeared to be connected with diet; they could be cured by changes in the food eaten, a fact which attracted the attention of physicians. For example, it has been known since 1804 that the disease of scurvy, so much feared in earlier times, could be avoided or cured by administration of lemon juice; the same is true of the beri-beri of Eastern countries, which can be cured by the addition of rice-polishings to the diet, as was shown in 1885 by Japanese and Dutch investigators. It was some time, however, before it was clearly understood that the food contained a definite compound responsible for the curative action.

Grijus, in 1901, was the first to give a clear definition of a deficiency disease or avitaminosis on this assumption.

The systematic scientific investigation of the vitamins only began, however, when it was learned how to produce deficiency diseases artificially in animals. Steps were taken in this direction by *Lunin* in 1881, in his experiments on the feeding of rats with a mixture of the organic and inorganic constituents of milk (Z. physiol. Chem. 5, 31). Little attention was, however, paid to these systematic experiments, until in 1897 *Eijkman* succeeded in producing artificial beri-beri (*Polyneuritis gallinarum*) in hens and pigeons by feeding them on polished ("over-milled") rice. Then followed the successful experiments of *Holst* and *Frölich* (1907) on the creation of scurvy in guinea-pigs, and *Stepp's* experiments on growth with mice (1909), and later the very significant results with rachitic rats (*McCollum*). Pioneering work on the investigations with animals was carried out by *Osborne* and *Mendel*, by *Hopkins*, by *McCollum*, *Windaus* and many others.

These animal experiments, which were considerably improved in technique in the course of years, were for some time the only indications of the isolation of the vitamins from the natural products. Later, however, characteristic chemical and physical reactions were introduced for their detection, and these were to some extent adapted to quantitative estimation. For example, vitamin A gives an intense blue colouration with antimony trichloride in chloroform (*Carr-Price* reaction: Biochem. J. 20 (1926), 497); vitamin C is distinguished by its strong reducing action towards silver salts (*Zilva*, ibid. 18 (1924), 182, 632) and 2:6-dichlorophenol-indophenol (*Tillmans* and co-workers, Z. Unters. Lebensm. 63 (1932), 241, 267, 276; *Tillmans* and *Hirsch*, N. 21 (1933), 314), while vitamins A and D have a characteristic ultraviolet absorption spectrum. By using these reactions, and with the aid of animal control experiments, the following vitamins have been isolated in the pure state in the years shown, their constitutions have been determined and some have been synthesised.

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[1] For further details see *Harris*, Vitamins in theory and practice, Cambridge U.P. 1937; *Sherman* and *Smith*, The Vitamins (Revised Edition), Am. Chem. Soc. Monographs.

Vitamin A: from liver oils.
Vitamin B_1: from rice polishings (1926), and later from yeast (1931).
Vitamin B_2: from whey and white of egg (1933).
Vitamin C: from adrenal cortex, oranges, cabbages etc. (1928, 1933).
Vitamin D_2: from ergosterol (1931).
Vitamin D_3: from tunny-fish liver oil (1936).
Vitamin E: from wheat germ oil (1936).

The existence of several other vitamins has been established by deficiency phenomena in experiments with animals.

a) FAT-SOLUBLE VITAMINS A, D AND E

In the study of the vitamins it is often found that several vitamins established by recent investigation were originally taken for one vitamin. This was the case with vitamins A and D; the mistake was aided by their mutual occurrence in cod liver oil, egg yolk, milk and butter, and by their similar solubility relationships, both being constituents of the unsaponifiable part of these fats and oils. Finally, however, it became clear that the two vitamins were distinct, since A was more sensitive to heat than D, and because the ergosterol of yeast could be converted into a vitamin D by ultraviolet irradiation.

1. VITAMIN A

The fat-soluble Growth Vitamin; Anti-xerophthalmic Vitamin

The fat-soluble vitamin A is particularly necessary for the growing organism. Thus xerophthalmia, an eye disease occurring in childhood, which was epidemic in Japan in 1904 and occurred amongst children in Denmark in the War, was shown to be a typical avitaminosis by animal experiments carried out upon young rats and mice by *Stepp* (1909), *McCollum* (1913), *Mellanby* and others. Not all animals fed upon a vitamin A-free diet develop the eye disease, but the stoppage in growth which always takes place in animal experiments shows that vitamin A is essential for normal growth; hence it is also known as the fat-soluble growth vitamin. Deficiency in vitamin A in children and adults causes a particular sensitivity towards a number of infectious diseases, a fact confirmed by numerous animal experiments. The so-called night-blindness (hemeralopia) also appears to be connected with a deficiency in vitamin A (*v. Euler* and *Hellström*, C. 1933 II 3152).

The chief source of vitamin A is the liver oils of fishes (cod liver oil), but these can show great variations in biological value (cf. *Seel*, Z. Vitaminforschung **1933** II 82). The content of vitamin A is also high in egg-yolk, milk and butter, while commercial animal fats (e.g. lard) and vegetable fats and oils do not contain any.

The further investigation and later isolation of the vitamin were considerably aided by the intense blue colour which it gives with $AsCl_3$ (*O. Rosenheim* and *Drummond*, Lancet **198** (1920), 862) or better with $SbCl_3$ (*Carr* and *Price*, 1926; see introduction) in $CHCl_3$ solution. This convenient and sensitive colour reaction is specific for vitamin A only in the absence of carotenoid pigments, since these substances also give a blue colour, indistinguishable except with the spectroscope.

Chief absorption of the blue solution formed with $SbCl_3$

by carotene	by vitamin A
590 mμ	572 mμ (and 606 mμ).

This forms the basis for a colorimetric estimation of the content of vitamin A solutions (*Brockmann* and *Tecklenburg*, Z. physiol. Chem. **221**, 117).

Vitamin A itself has an absorption band in the ultraviolet at 328 mμ, a fact used as an indication in the isolation process.

Relationship of the Carotenoids to Vitamin A

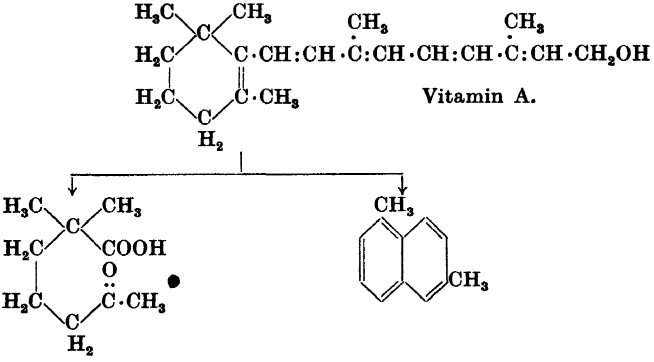
Great theoretical and practical interest attaches to the discovery (*Moore*, Biochem. J. **23** (1929), 803; *v. Euler* and *Rydbom*, C. 1930 I 3324) that carotenoid pigments can be converted in the liver into vitamin A; this is particularly the case with α-, β- and γ-carotene, the deeply-coloured hydrocarbons, $C_{40}H_{56}$, which occur chiefly in the carrot, and with kryptoxanthin, $C_{40}H_{56}O$ (see Natural Colouring Matters, p. 412):

$$C_{40}H_{56}+2H_2O=2C_{20}H_{30}O\,.$$

The animal organism can store vitamin A in various tissues and organs, particularly in the liver. The manner in which vitamin A takes part in the metabolism is not yet known.

Isolation. All the experiments directed towards the isolation of vitamin A originated with the discovery of *McCollum* and *Davis* (J. Biol. Chem. **19** (1914), 245) that vitamin A (and D) remained in the unsaponifiable fraction of cod liver oil. The liver oil (halibut liver oil is particularly rich [*Karrer*]) is saponified with boiling alcoholic potash with exclusion of air, and the unsaponified part extracted with ether. The separation of the sterols, by precipitation with digitonin or by cooling a methyl alcoholic solution to —60°, leaves a yellowish oil, which is a concentrate of vitamin A with a little D. Further purification is carried out by adsorption on aluminium hydroxide (*Karrer* and *Morf*, Helv. **14**, 1033; *Karrer*, *Morf* and *Schöpp*, ibid. 1036, 1431), or by high vacuum distillation at 10^{-5} mm. (*Heilbron* and co-workers, Biochem. J. **26** (1932), 1178). The oily preparations so obtained are active in growth experiments in doses of 0·5 γ and 0·1 γ respectively.

Vitamin A, $C_{20}H_{29}OH$, is a pale-yellow oil, m.p. 7–8° (*Holmes* and *Corbet*, Am. **59**, 2042); its acetyl, benzoyl and *p*-nitrobenzoyl derivatives are not crystalline. Its absorption spectrum shows a main band in the ultraviolet at 328 mμ. It gives an intense blue colouration with $AsCl_3$ and particularly with $SbCl_3$ in chloroform solution. When oxygen is excluded it can be boiled for a long time without change; it is immediately destroyed by bromine and oxidising agents. Ozonolysis leads to the isolation of geronic acid, showing the presence of a β-ionone ring (*Karrer*, *Morf* and *Schöpp*, Helv. 4, 1036, 1431) (see also β-carotene, p. 412). On dehydrogenation with selenium a second ring is formed and two methyl groups and part of the side-chain are eliminated, giving 1:6-dimethyl-naphthalene (*Heilbron*, *Morton* and *Webster*, Biochem. J. **26** (1932), 1194):



Vitamin A.

Geronic acid

The similarity in the formulae of vitamin A and the carotenoids is mentioned on p. 421. It is important to note that in agreement with the formulae, β-carotene, which by central fission can give two mols. of vitamin A, is the most active in animal experiments. This conversion into vitamin A appears to depend upon the presence of at least one ionone ring; hence the purely aliphatic polyene, lycopene, $C_{40}H_{56}$ (p. 412), which often occurs with the carotenes, is not a provitamin A, and kryptoxanthin, $C_{40}H_{56}O$ (p. 412), is the only xanthophyll which shows vitamin A activity. These facts are of great practical significance for those peoples whose chief food is maize.

2. VITAMINS D

Antirachitic Vitamins

The fat-soluble D vitamins influence the mineral metabolism, particularly the calcium phosphate metabolism. They are of great practical significance, since a deficiency can lead in the first few years of life to a considerable and permanent deformation of the bones (rickets). The formation and preservation of the teeth also appear to be influenced by these vitamins. Hence it is clear that the D vitamins are of special significance for the small child and the growing animal; it is comparitively seldom that adults show signs of any deficiency in these vitamins, but the occasional occurrence of osteomalacia, the rickets of adults, shows that even in maturity the antirachitic vitamins are not entirely unnecessary.

The avitaminosis concerned here is rickets, although the disease doubtless has more complex causes, like the avitaminoses connected with other vitamins. Its chief symptom is the lack of hardening of the growing bone-tissue by the inclusion of calcium phosphate; the bones remain soft and suffer marked deformations. Rickets is shown clinically by a deficiency of phosphates in the blood, and by the very typical X-ray diagram of the growing part of the bones. Rats are used for the animal experiments, since they readily develop the symptoms of rickets when fed on a suitable vitamin D free diet.

It has long been known that rickets can be decreased or cured by two factors: by irradiation with ultraviolet light, and by the addition of cod liver oil to the diet. The latter fact indicated at once that the curative factor might be present in a fat; but the curative effect of ultraviolet light did not seem to favour the presence of an avitaminosis. Today, as a result of many years of investigation, we know that it is an inactive "provitamin" that is converted into vitamin D by the irradiation of the skin or food with ultraviolet light, while the liver-oils of fishes, especially cod liver oil and halibut liver oil, contain an antirachitic vitamin in the active form. The vitamin is also found in small quantities in milk, butter and yolk of egg.

The first attempts to isolate the vitamin were carried out upon cod liver oil, and they indicated the properties important for the isolation, viz. its presence in the unsaponifiable fraction of cod liver oil, and its complete analogy with the sterols in solubility; it differs from these, however, by the fact that it is not precipitated by digitonin (*Nelson* and *Steenbock*, J. Biol. Chem. **64** (1925), 299).

A discovery of the greatest importance for the further development of the problem was that the vitamin is contained in certain fats, or in their sterol fractions, in the form of an inactive "provitamin", which is converted by ultraviolet light into a vitamin D (*Steenbock*, Science **60** (1924), 224; *Hess*, ibid. 269; *Steenbock* and *Nelson*, J. Biol. Chem. **62** (1924), 209). The isolation was thereby coupled with the study of this mother substance. Since cholesterol, after repeated crystallisation, still developed vitamin D activity on ultraviolet irradiation, it was at first thought that this sterol was the provitamin (*Hess*, *Weinstock* and *Sherman*, J. biol. Chem. **67** (1926), 413). This idea was soon shown to be erroneous, since cholesterol purified through its dibromide invariably gave an inactive product on irradiation (*Hess* and *Windaus*, Proc. Soc. Exp. Biol. Med. **24** (1927), 369). The provitamin, now established as a substance accompanying cholesterol, could also be completely removed by other means, e.g. oxidation with permanganate in acetone or adsorption on animal charcoal.

The tenacity with which the provitamin accompanied cholesterol indicated that it was very probably one of the sterols which is sensitive to oxidation. At this stage a considerable advance was made by the measurement of the ultraviolet absorption spectrum of cholesterol containing the provitamin; this showed that ordinary cholesterol contained $^1/_{60}\%$ of an impurity with a selective absorption in the long ultraviolet; the absorption maxima were at 293·5, 281·5 and 265 mμ, and were displaced towards the shorter ultraviolet by irradiation (*Hess* and *Weinstock*, Lancet **210** (1926), 12; *Hess*, J. Amer. Med. Assoc. **84** (1925), 1910, Deut. Med. Woch. **52** (1926), 577). This showed at the same time that the provitamin must be a strongly unsaturated sterol; attention was at once directed towards ergosterol, $C_{28}H_{44}O$, m.p. 165°, prepared from ergot of rye (*Tanret*, C. r. **147**, 75), and later from other fats derived from fungi, especially from yeast fat (*McLean* and *Thomas*, Biochem. J. **14** (1920), 483) (see Sterols, and *Windaus* and *Hess*, Nachr. Ges. Wiss. Göttingen, **1926**, 175; *Windaus*, Chem.-Ztg. **51** (1927), 103).

Ergosterol did in fact agree in its ultraviolet absorption with the provitamin accompanying cholesterol (*Pohl*, N. **15** (1927), 433; *Windaus* and *Hess*, loc. cit.; *Rosenheim* and *Webster*, Biochem. J. **21** (1927), 389; Lancet **213** (1927), 622; *Heilbron*, *Kamm* and *Morton*, Biochem. J. **21** (1927), 78), and also in its sensitivity towards oxidising agents, and its ease of adsorption by active charcoal; further, irradiation caused a displacement of the absorption towards the shorter ultraviolet, with the formation of vitamin D_2 (calciferol), a substance still active in minimal doses, and no longer precipitated by digitonin.

The isolation of the pure crystalline vitamin D_2 from the oily irradiation product of ergosterol was a difficult problem and after several years' effort was first achieved in 1930 (*Bourdillon* and co-workers, Proc. Roy. Soc. London **107** B, (1930), 76: 1931, **108** B, 340; 1932, **109** B, 488; *Windaus* and co-workers, Ann. **489**, 252, 269; **492**, 226; **493**, 250).

The compound was called calciferol by the English workers, and at first vitamin D_1 by the German. The name was later changed to vitamin D_2 when it was realised that the preparation called D_1 was a molecular compound of the true vitamin and its irradiation product, lumisterol.

Vitamin D_2 (calciferol), $C_{28}H_{44}O$, m.p. 115–116°; $[\alpha]_D + 103°$, $[\alpha]_{546} + 124°$ (alcohol); chief absorption band at 265 mμ; it contains three rings and four double bonds; one of the latter is in the side-chain in the same position as in ergosterol, and two are conjugated. Vitamin D_2 is not precipitated by digitonin, and can be distilled unchanged in high vacuo. 3:5-Dinitrobenzoate m.p. 148–149°, $[\alpha]_D + 55°$. Dihydrovitamin D_2, $C_{28}H_{46}O$, m.p. 65°, $[\alpha]_D + 8{\cdot}0°$, obtained by reduction of the vitamin with Na and alcohol, is inactive (*Windaus* and co-workers, Ann. **492**, 226; other references will be found in this paper). Heating the vitamin to 190° causes isomerisation with formation of an inactive, non-poisonous molecular compound (m.p. 122–124°) of isopyrovitamin (m.p. 112–115°, precipitated by digitonin) and pyrocalciferol, m.p. 94–95° (*Busse*, Z. physiol. Chem. **214**, 211). Vitamin D_2 preparations are used therapeutically and prophylactically.

The vitamin D_2 obtained by the irradiation of the provitamin ergosterol was for some years the only compound with antirachitic activity known. It was then shown, however, that 7-dehydro-cholesterol, $C_{27}H_{43}OH$ (*Windaus*, *Lettré* and *Schenck*, Ann. **520**, 98) was converted by ultraviolet irradiation (*Windaus*, *Schenck* and *v. Werder*, Z. physiol. Chem. **241**, 100) into a new antirachitic substance, which is called *vitamin D_3* (3:5-dinitrobenzoate m.p. 129°; allophanate m.p. 173°).

The same vitamin D_3 has been isolated with great difficulty as the 3:5-dinitrobenzoate from tunny-fish liver oil (*Brockmann*, Z. physiol. Chem. **241**, 104). This shows that the antirachitic constituent of this fish liver oil is derived from cholesterol, and not from ergosterol. It should be noted that 7-dehydro-sitosterol also becomes antirachitic on irradiation (*Wunderlich*, ibid. 116). This shows that there are several provitamins D, and that they are in all probability the 7-dehydro-sterols which accompany natural sterols, and are converted by irradiation into the various antirachitic vitamins.

The determination of the constitution of the D vitamins obtained by the irradiation of various provitamins was of the greatest importance, and was carried out with ergosterol (provitamin D_2).

It was shown by *Windaus* and his collaborators (Ann. **499**, 188; Z. physiol. Chem. **215**, 183) that the photochemical change of ergosterol produces a series of intermediates and by-products, of which the following appear to form a series, each being an isomer of the original sterol:

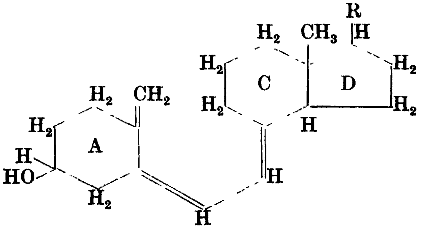
> Ergisterol → lumisterol → tachysterol → vitamin D_2 → suprasterol → toxisterol (an inactive, somewhat poisonous, product of over-irradiation).

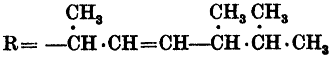
The first product of the irradiation, **lumisterol,** $C_{28}H_{44}O$, m.p. 118°, $[\alpha]_D + 191{\cdot}5°$ (acetate m.p. 100°, $[\alpha]_D + 162{\cdot}8°$), is a stereoisomer of ergosterol, differing from the latter in the spatial arrangement at C_{10} of the sterol skeleton (see p. 553) *Dimroth*, Ber. **69**, 1123; *Heilbron*, *Spring* and *Stewart*, J. **1935**, 1221). Then follows a decisive step in the direction of the vitamin by the conversion into tachysterol, $C_{28}H_{44}O$, $[\alpha]_D - 70°$, an oil which contains only three rings, and hence four double bonds. Thus one ring of ergosterol or lumisterol is opened by the action of ultraviolet light with the formation of a new double bond (*Lettré*, Ann. **511**, 280). This important fact was confirmed by the following results: (1) tachysterol is no longer dehydrogenated by Se at 320° to Diels' hydrocarbon, $C_{18}H_{16}$ (see p. 553), which is characteristic of the tetracyclic sterol skeleton; (2) catalytic hydrogenation of derivatives of tachysterol and titration with perbenzoic acid show the presence of four double bonds.

Vitamin D_2 (calciferol), $C_{28}H_{44}O$, is closely related in structure to tachysterol, and differs only in the position of the double bonds. Both substances are reduced by Na and alcohol to the same dihydro-compound, in which three double bonds can still be detected with perbenzoic acid and by refractometric measurements (*Reichel* and *Deppe*, Z. physiol. Chem. **239**, 143; *Müller*, ibid. **233**, 223). Vitamin D_2 itself takes up four mol. of hydrogen in micro-hydrogenation.

It is ring B (see p. 553) of ergosterol that has been opened, between C_9 and C_{10}; this was proposed by *Lettré* (Z. angew. Chem. **48**, 152) and *Schmidt* (Ber. **68**, 795) on the basis of the double bond rule of the latter, as being the ring bond easiest to break.

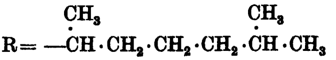
The experimental proof of the position where the ring has opened was brought forward simultaneously by *Heilbron* and his collaborators (Nature **135** (1935), 1072) and by *Windaus* and *Thiele* (Ann. **521**, 160); the latter also determined the position of the new double bond, and hence established completely the constitution of vitamin D_2 (calciferol). From their experiments which are briefly described below, *Windaus* and *Thiele* (loc. cit.) proposed the following structural formula. Vitamin D_3 was later given a similar formula (*Windaus*, *Schenck* and *v. Werder*, Z. physiol. Chem. **241**, 100; *Brockmann*, ibid. 104).





$$R = -\overset{CH_3}{\dot{C}H}\cdot CH{=}CH-\overset{CH_3}{\dot{C}H}\cdot\overset{CH_3}{\dot{C}H}\cdot CH_3$$

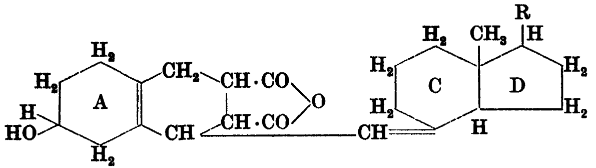
Vitamin D_2 (calciferol)



$$R = -\overset{CH_3}{\dot{C}H}\cdot CH_2\cdot CH_2\cdot CH_2\cdot\overset{CH_3}{\dot{C}H}\cdot CH_3$$

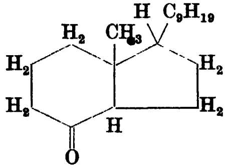
Vitamin D_3

The decisive results in favour of this structure were obtained by ozonolysis of the maleic anhydride adduct of vitamin D_2, or of its dihydro-derivative, and the dehydrogenation of the same products with Pd or Se.

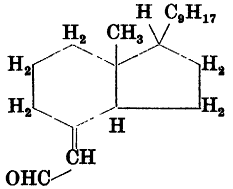


$R=C_9H_{17}$: vitamin adduct
$R=C_9H_{19}$: dihydrovitamin adduct

In the ozonolysis (*Windaus* and *Thiele*, Ann. **521**, 165), rings C and D of the original sterol skeleton are obtained as the saturated ketone $C_{19}H_{34}O$ (semicarbazone m.p. 225°; oxime m.p. 129·5°), which can only have the following formula:



$C_{19}H_{34}O$



Aldehyde, $C_{21}H_{34}O$

The other half of the molecule of vitamin D_2, including ring A of the original sterol skeleton, can be isolated by dehydrogenation of the adduct with Pd, as naphthalene or β-naphthoic acid, or with Se as 2:3-dimethyl-naphthalene, in good agreement with the above formula for the maleic anhydride adduct.

The same structure follows from the experiments of *Heilbron* and his collaborators. They obtained (loc. cit.) by the chromic or permanganate oxidation of calciferol itself or its acetate an oily, αβ-unsaturated aldehyde, $C_{21}H_{34}O$ (semicarbazone m.p. 242°), for which they have established the formula shown above (*Heilbron*, *Jones*, *Sament* and *Spring*, J. **1936**, 905). Finally, they have proved the presence of the semicyclic methylene group by detecting the formaldehyde formed in the ozonolysis of calciferol (J. **1936**, 905).

The physiologically inactive products obtained by over-irradiation (suprasterols I and II, and toxisterol) seem to have undergone ring closure again to a tetracyclic system.

3. VITAMIN E

The Anti-sterility Vitamin

The first indication of the existence of this fat-soluble vitamin came from experiments on rats and mice (*Mattill* and *Conklin*, J. Biol. Chem. 44 (1920), 137; *Evans* and *Bishop*, J. Metabol. Res. 1 (1922), 319, 335). It was shown that animals fed exclusively on milk or on a diet containing all classes of foodstuffs and known vitamins, could no longer reproduce after some time. This loss concerns both the female animal, in which during vitamin E deficiency the foetus dies after an initial normal development and is re-absorbed by the mother's organism, and also the male animal, which loses its procreative faculty.

In the case of female animals fertility can be restored by administering vitamin E concentrates, whereas this is rarely possible with male animals. This may be due to the fact that deficiency does not became apparent in males until actual degeneration of the reproductive organs has set in. Whether partial vitamin E deficiency is widespread in human beings is not known, but successful experiments have been reported by various workers in the treatment of habitual abortion in women by the use of vitamin E concentrates (*Vogt-Möller*, Lancet **1931**, II, 182).

The chief sources of vitamin E are green leaves (salads), the germs of plant seeds and the oils expressed from such seeds, e.g. wheat, maize, oats and cotton seed oils and rice germ; small quantities are also contained in milk and butter, while cod liver oil and yeast fat appear to be absolutely free of it.

Vitamin E remains in the unsaponifiable part of the oils mentioned above, but unlike many sterols it is not precipitated by digitonin. It is very stable to heat and may be distilled in a high vacuum at about 230°, but it is attacked by peroxidic oxygen; it is therefore destroyed when the oils turn rancid. Vitamin E activity seems to be shown by several closely related substances. *Evans, Emerson* and *Emerson* (J. Biol. Chem. **113** (1936), 319) isolated two active compounds — tocopherols — from wheat germ oil as crystalline allophanates, and this result has been confirmed by various groups of workers (*Fernholz*, Am. **59**, 1154; *Todd, Bergel, Waldmann* and *Work*, Nature **140** (1937), 361; *Todd, Bergel* and *Work*, Biochem. J. **31** (1937), 2247; *John*, Z. physiol. Chem. **250**, 11; *Drummond* and *Hoover*, Biochem. J. **31**, 1852). The tocopherols themselves are oils of approximate formula $C_{28-30}H_{48-52}O_2$, one oxygen atom being present as a hydroxyl group and the other probably in an ether linkage. They appear to be derivatives of duroquinol or ψ-cumoquinol, but their detailed structure is not yet known (*Fernholz*, loc. cit.; *John*, loc. cit.; *Bergel, Todd* and *Work*, Chem. and Ind. **56** (1937), 1054; *McArthur* and *Watson*, Science **86** (1937), 35). Condensation of trimethyl hydroquinone with phytyl bromide (*Karrer, Fritzsche, Ringier* and *Salomon*, Helv. **21**, 820), or with phytol (*Bergel, Jacob, Todd* and *Work*, Nature **142** (1938), 36), gives a compound which is either a chroman or a coumaran and is probably identical with *dl* α-tocopherol.

b) THE WATER-SOLUBLE VITAMINS: B GROUP AND C

Vitamins of the B group

The investigation of this group originated from the disease of beri-beri, the connection of which with a diet of polished rice, and the cure for which with rice-polishings or their extract, was shown chiefly by Japanese and Dutch physicians. The animal experiments of *Eijkman* (1897) on pigeons, chicken and other birds were particularly important for the scientific development of this group of vitamins, showing with absolute certainty the vitamin-nature of the curative substance. The further development of this group, however, has become exceedingly complicated. It appeared originally as though one water-soluble vitamin (anti-beri-beri or growth promoting vitamin) was necessary for the avoidance of beri-beri and other similar diseases, and for the preservation of normal growth in animals, but numerous animal experiments (chiefly in 1925—1930) have since shown that the original vitamin fraction used contained at least two vitamins, now distinguished as vitamin B_1 (antineuritic, anti-beri-beri), and vitamin B_2 (growth-promoting). Further investigations and very careful experiments with animals make it probable that several other vitamins of the B group exist. It is important to note that all the vitamins mentioned here occur in yeast and are distinguished by their varying stability towards alkali and heat.

1. VITAMIN B_1. ANEURIN

The Anti-neuritic, anti-beri-beri Vitamin (Oryzanin)

As mentioned above, the existence of vitamin B_1 became known because of the disease beri-beri, which occurs chiefly in the riceconsuming countries of Japan, China, India and Malaya. The Japanese physician *Takaki* (1885) was the first to discover the fact that a change in diet can cure this disease, which at that time was very prevalent. This showed clearly that beri-beri was an avitaminosis, the chief cause of which was a deficiency in vitamin B_1. Intensive scientific investigation began with the discovery of *Eijkman* (1897) that hens and pigeons develop a disease (*Polyneuritis gallinarum*) very similar in its symptoms to human beri-beri when they are fed on polished rice. With the aid of these animal experiments the occurrence and chief properties of the vitamin were investigated.

Chief sources: rice-polishings, yeast, cereals, particularly in the germ of the seed, and liver; minute quantities are found in many foodstuffs, especially vegetables.

Solubility and stability to heat. Since aqueous extracts, and extracts with 70% alcohol, of yeast and rice-polishings show a curative effect, the vitamin is soluble in water and dilute alcohol; it is also soluble in acetic acid; it is insoluble in ether, benzene and petroleum ether. Its stability towards heat was determined by animal experiments, and showed that vitamin B_1 was not appreciably changed by several hours boiling in aqueous solution; at a higher temperature (120–130° in an autoclave), however, it deteriorated in a short time, and continued heating completely destroyed it. This is its chief distinction from vitamin B_2, which is more stable to heat. Autoclaved yeast no longer shows a curative effect for beri-beri. The vitamin itself is stable to high concentrations of hydrogen ion, but is rapidly destroyed by alkali. Its purification is aided by the fact that it is adsorbed from aqueous solution by various agents, e.g. silica gel, alumina, fullers' earth and animal charcoal.

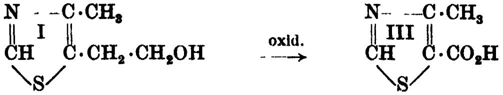
Isolation of crystalline vitamin B_1. ***Funk*** attempted to prepare the pure vitamin in 1911, but it required almost 20 years' work before attempts were successful. ***Jansen*** and ***Donath*** were the first to isolate from rice-polishings the vitamin in a crystalline state as its hydrochloride (Koninkl. Akad. Wetensch. Amsterdam **35** (1926), 923). Several years later (1931) ***Windaus*** and his collaborators prepared the vitamin hydrochloride from yeast, and established its sulphur content, previously overlooked (Z. physiol. Chem. **204**, 123). Since then the vitamin has often been obtained pure (*van Veen*, Rec. **49** (1930), 1178; ***Ohdake***, Bull. Agri. Chem. Soc. Japan **8** (1932), 11; Proc. Imp. Acad. Tokyo **8** (1932), 179; ***Kinnersley***, ***O'Brien*** and ***Peters***, Biochem. J. **27** (1933), 232; ***Williams***, ***Waterman*** and ***Keresztesy***, Am. **56**, 1187). The yields first obtained were very small, but later workers have improved the technique; thus Ohdake got 1·6 g. of the hydrochloride from 11,500 kg. of rice polishings, but Williams got 0·45 g. from 100 kg.

Vitamin B_1, aneurin, is only known in the form of its salts. The free base, which would be quaternary, cannot be obtained pure; its formula would be $C_{12}H_{18}O_2N_4S$. The chief salt that has been investigated is the chloride-hydrochloride, $C_{12}H_{17}ON_4SCl \cdot HCl$, m.p. 250° decomp.; picronolate, m.p. 229° decomp.; aurichloride, m.p. 198° decomp. The salts show absorption bands in alcohol between 360 and 310, and 280 and 250 mμ; it contains an alcoholic OH group (*van Veen*, Rec. **51** (1932), 265), a NH_2-group (***Williams***, Am. **57**, 1093), and two tertiary N atoms; but COOH, CO, NH, OCH_3 and NCH_3 are not present.

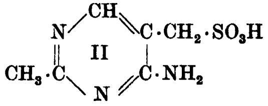
Considerable insight into the structure of the molecule was obtained by ***Williams*** and his collaborators (Am. **57**, 229, 536, 1093) who found that vitamin B_1 in a solution of acid sodium sulphite undergoes fission according to the equation:

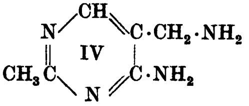
$$C_{12}H_{17}ON_4SCl \cdot HCl + Na_2SO_3 \rightarrow C_6H_9ONS(I) + C_6H_9O_3N_3S(II) + 2\,NaCl$$

The fission product (I) was synthesised by ***Clarke*** and ***Gurin*** (Am. **57**, 1876) and shown to be 4-methyl-5-β,hydroxyethyl-thiazole (I). On oxidation it yielded 4-methyl-thiazole-5-carboxylic acid (III); this acid, although unrecognised at the time, had previously been obtained by oxidation of the vitamin with nitric acid (*Windaus*, *Tschesche* and *Grewe*, Z. physiol. Chem. **228**, 27).

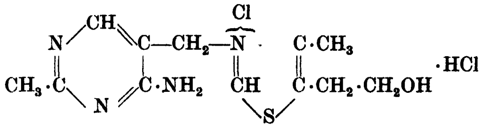


Williams (Am. **57**, 229) had concluded that the second fission product (II) was a pyrimidine sulphonic acid because of the similarity of its absorption spectrum with that of 6-aminopyrimidine sulphonic acid, and suggested that the vitamin was a pyrimidyl-thiazolium salt. It was later shown that this suggestion was erroneous (*Todd* and *Bergel*, Nature **138** (1936), 76; J. **1936**, 1559) and that the second fission product was identical with synthetic 2-methyl-4-amino-pyrimidine-5-methylsulphonic acid (II) (*Williams*, Am. **58**, 1063; *Cline*, *Williams*, *Ruehle* and *Waterman*, Am. **59**, 530).





The structure of the two fission products having been established it follows that vitamin B_1 is a (pyrimidyl-5-methyl)-thiazolium salt (*Williams*, loc. cit.). A similar conclusion was arrived at independently by *Grewe* (Z. physiol. Chem. **242**, 92) who showed that the synthetic base (IV), 2-methyl-4-amino-5-aminomethyl pyrimidine, is identical with the base produced by mild oxidation of the vitamin with barium permanganate (*Windaus*, *Tschesche* and *Grewe*, ibid. **237**, 98).



Vitamin B_1 (aneurin)

The constitution of this important vitamin has since been established by synthesis. This can be carried out by condensing 2-methyl-4-amino-5-bromomethyl-pyrimidine with 4-methyl-5-β,hydroxyethyl-thiazole (*Williams* and *Cline*, Am. **58**, 1504; *Cline*, *Williams* and *Finkelstein*, ibid. **59**, 1052), and also by condensing 2-methyl-4-amino-5-thioformamidomethyl-pyrimidine with α-chloro-γ-acetoxypropyl ketone (*Todd* and *Bergel*, J. **1937**, 364). Methods similar to both of these were also used by *Andersag* and *Westphal* (Ber. **70**, 2035). Various isomers and analogues of the vitamin have been synthesised (*Todd* and *Bergel*, J. **1936**, 1559; **1937**, 1504; *Andersag* and *Westphal*, loc. cit.).

Vitamin B_1 is colourless, but when it is oxidised under mild conditions with potassium ferricyanide, it is converted into a yellow substance, thiochrome, which has an intense blue fluorescence in solution. The formula of thiochrome is $C_{12}H_{14}ON_4S$, m.p. 226°, hydrochloride, m.p. 221° (*Barger*, *Bergel* and *Todd*, Ber. **68**, 2257); it has been synthesised (*Todd*, *Bergel*, *Fraenkel-Conrat* and *Jacob*, J. **1936**, 1601). The same substance has also been isolated from yeast (*Kuhn*, *Wagner-Jauregg*, *van Klaveren* and *Vetter*, Z. physiol. Chem. **234**, 196). Its formation can be used in order to estimate vitamin B_1. Thiochrome has no vitamin activity (see Natural Colouring Matters, p. 477).

2. VITAMIN B_2

If rats are fed on a diet containing vitamins A and D, aneurin (vitamin B_1) and a yeast extract artificially freed from vitamin B_2, the growth ceases (*Kuhn*, *György* and *Wagner-Jauregg*, Ber. **66**, 317).

Vitamin B_2 is more stable to heat than B_1, for yeast, which contains both vitamins, still shows vitamin B_2 activity after autoclaving at 120° at pH 5, while the B_1 activity is destroyed; at pH 8, however, the B_2 activity disappears.

Vitamin B_2 is present in the lyochromes, the water-soluble colouring matters with a yellowish green fluorescence which are contained in whey, white of egg, yeast, liver, heart and kidney (*Kuhn* and collabs., Ber. **66**, 317, 576, 1034, 1577, 1950; *Ellinger* and *Koschara*, ibid. 315, 808, 1411). Of these, lactoflavin has been investigated in detail; it can be obtained crystalline from whey, 5.400 litres yielding 1 g. of the colouring matter (*Kuhn*, *György* and *Wagner-Jauregg*, Ber. **66**, 1034). Lactoflavin was tested with rats and found to be biologically active in the presence of other vitamins of the group (*György*, *Kuhn* and *Wagner-Jauregg*, N., **21**, 560; *Kuhn*, *Rudy* and *Wagner-Jauregg*, Ber. **66**, 1950; *György*, *Kuhn* and *Wagner-Jauregg*, Klin. Woch. **12**, 1241).

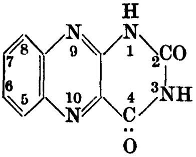
It should be noticed that a yellow oxidation enzyme isolated from yeast by *Warburg* and *Christian* (Biochem. Z. **254** (1932), 438) is a compound of vitamin B_2 (lactoflavin), with one mol. of phosphoric acid and a protein component. Since the yellow enzyme is also found in the animal body, it is possible that the animal cells require vitamin B_2 for the synthesis of the yellow enzyme, and that the vitamin is used in this way for oxidation-reduction processes.

The fissions described below were first carried out on the coloured component of the yellow enzyme.

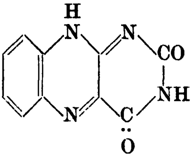
Lactoflavin, $C_{17}H_{20}O_6N_4$, m.p. 292° decomp. (corr.), $[\alpha]_D + 110°$ (NaOH), after the addition of borax $[\alpha]_D + 360°$ (tetra-acetyl derivative m.p. 242° decomp.), forms brownish-orange needles. Chief absorption bands in aqueous solution: 445, 365, 265, 220 mμ (isolation from whey, *Kuhn* and collaborators, Ber. **66**, 1037, 1954); it is readily soluble in water and stable towards acids, but changed by alkalis. With Ag and Tl salts it forms difficultly soluble salts, which can be advantageously used for its purification. Mild reduction (Na hydrosulphite, $Pt + H_2$, or Zn dust in acid solution) gives the colourless leuco-lactoflavin, which is converted back into lactoflavin by atmospheric oxidation. The action of light upon lactoflavin in the presence of alkali causes the fission of a hydroxylated side-chain, $C_4H_8O_4$, and gives the optically inactive lumiflavin, $C_{13}H_{12}O_2N_4$, m.p. 328°, which is soluble in chloroform. The action of hot 2 N. NaOH hydrolyses lumiflavin into one mol. of urea and a carboxylic acid $C_{12}H_{12}O_3N_2$, m.p. 215°, which can be decarboxylated to a pale yellow compound, $C_{11}H_{12}ON_2$, m.p. 174° (*Warburg* and *Christian*, Biochem. Z **263**, 228; **266**, 377; *Kuhn* and *Wagner-Jauregg*, Ber. **66** 1577; *Kuhn*, *Rudy* and *Wagner-Jauregg*, ibid. 1953; *Kuhn* and *Rudy*, Ber. **67**, 892; *Kuhn* and *Bar*, ibid. 898). The latter compound, a lactam, is converted by hot caustic soda into the base $C_9H_{14}N_2$, by the addition of 2H O and the elimination of glyoxylic acid (*Kuhn*, Z. angew. Chem. **49**, 6). These relationships are given below:

$$\begin{array}{l}
\text{Lactoflavin} \rightleftarrows \text{Leucolactoflavin} \\
C_{17}H_{20}O_6N_4 \\
\quad\downarrow \text{light, } O_2\text{, alkali} \\
\text{Lumiflavin: } C_{13}H_{12}O_2N_4 + C_4H_8O_4 \\
\quad\downarrow 2\text{ n NaOH (hot)} \\
C_{12}H_{12}O_3N_2 + CO(NH_2)_2 \\
\quad\downarrow \text{Sublimation} \\
C_{11}H_{12}ON_2 + CO_2\ . \\
\quad\downarrow \text{NaOH} + 2H_2O \\
\textbf{Base } C_9H_{14}N_2 + \text{Glyoxylic acid.}
\end{array}$$

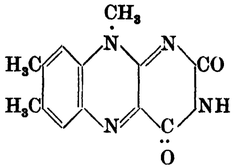
Soon after the discovery of these reactions, *Kuhn* and his collaborators drew attention to the similarities which lactoflavin shows with alloxazine derivatives (see formula) (Ber. **66**, 1579; **67**, 898). By an adaptation of a synthesis of alloxazine which had been long known, lumiflavin itself was synthesised, and its constitution established (*Kuhn, Reinemund* and *Weygand*, Ber. **67**, 1460). This synthesis also established the nature of the ring-system present in vitamin B_2.



Alloxazine



Iso-alloxazine flavin

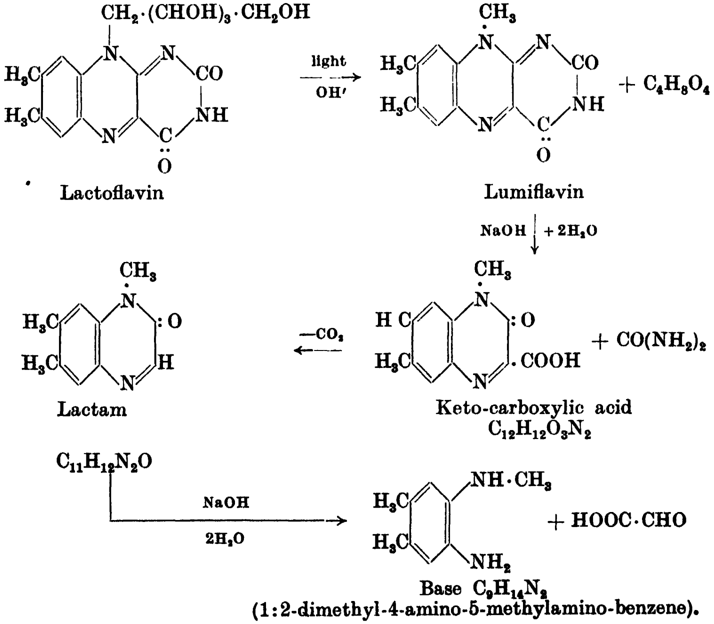


Lumiflavin,
6:7:9-trimethyl-flavin.

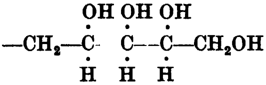
The conversion of lactoflavin into lumiflavin is accompanied, as has been mentioned, by the elimination of a side-chain which contains four hydroxyl groups, and the formation of a NCH_3 group. On the basis of the synthesis of lumiflavin it was shown (*Kuhn, Rudy* and *Wagner-Jauregg*, Ber. **66**, 1950)

1) that the side-chain could only be attached to N-atom 9;
2) that the eliminated group is a tetrahydroxy-butyl residue (*Kuhn, Rudy* and *Weygand*, Ber. **66**, 1951; formation of an acetone compound, idem, Ber. **68**, 625).

Neglecting the spatial arrangement of the three asymmetric C-atoms contained in the side-chain, vitamin B_2 (lactoflavin), and the reactions described, can be represented as follows:



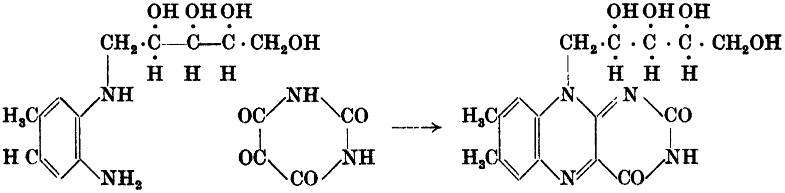
The last point, the spatial configuration of the group $C_4H_8O_4$, was settled by the synthesis of lactoflavin; the proposal of *Kuhn, Rudy* and *Weygand* (Ber. **68**, 625) was shown to be correct, the residue having the configuration of *d*-ribose.



$$-CH_2-\overset{OH}{\underset{H}{C}}\ \ \overset{OH}{\underset{H}{C}}-\overset{OH}{\underset{H}{C}}-CH_2OH$$

The synthesis of lactoflavin was carried out simultaneously by *Karrer* and his collaborators (Helv. **18**, 522, 1435) and by *Kuhn* and his collaborators (Ber. **68**, 1765), by an extension of the synthesis of the alloxazine ring system.

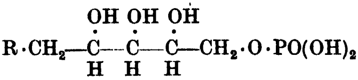
The starting material for the synthesis was 4:5-dimethyl-N-(*d*)-ribityl-o-phenylene diamine, which was coupled with alloxan to give the iso-alloxazine (lactoflavin); the addition of boric acid (*Kuhn* and *Weygand*, Ber. **68**, 1282) considerably increased the yield:



6:7-Dimethyl-9-(d)-ribitylflavin = lactoflavin

The synthesis of lumiflavin, mentioned above, was by the same method, starting with N-methyl-4:5-dimethyl-o-phenylene diamine (*Kuhn* and co-workers, Ber. **67**, 1460).

As has been stated above (p. 572), vitamin B_2 forms with phosphoric acid and a protein the yellow enzyme which was isolated by *Warburg* from yeast, and obtained crystalline by *Theorell* (Biochem. Z. **272** (1934), 155; **275** (1934), 37, 344, 416; **278** (1935), 263). In this connection, particular interest attaches to lactoflavin-5′-phosphoric acid,



$$R\cdot CH_2-\overset{OH}{\underset{H}{C}}-\overset{OH}{\underset{H}{C}}-\overset{OH}{\underset{H}{C}}-CH_2\cdot O\cdot PO(OH)_2$$

R=dimethyl-iso-alloxazine

This has been synthesised (*Kuhn, Rudy* and *Weygand*, Ber. **69**, 1543), and has been shown to be identical with cytoflav; this substance was first obtained in an impure state from muscular tissue by *Banga* and *Szent-Györgyi* (Biochem. Z. **246** (1932), 212), who recognised its significance in cell respiration.

The coupling of lactoflavin-5′-phosphoric acid, the constitution of which is completely known, with the protein obtained by the fission of the natural yellow ferment, gives a non-dialysable chromoproteid which behaves exactly like the natural enzyme (*Kuhn* and *Rudy*, Ber. **69**, 1974). This synthesis is the first artificial preparation of an enzyme to be achieved, and it provides some support for the idea first put forward by Willstätter that many enzymes consist of an active group and a colloidal carrier of high molecular weight.

8. OTHER VITAMINS OF THE B GROUP

Although complete characterisation of the vitamins of the B group has not yet been accomplished, it is certain that, in addition to B_1 and B_2, rats require for maximal growth at least two more vitamins of this group (*Lepkovsky, Jukes* and *Krause*, J. Biol. Chem. **115** (1936), 557; *Edgar* and *Macrae*, Biochem. J. **31** (1937), 886). Apart from B_1, there seems to be a B_2-complex which consists of at least three factors (*Harris*, Biochem. J. **31** (1937), 1414). These are: (1) lactoflavin, (2) vitamin B_6, which prevents dermatitis in rats, (3) the P—P (pellagra preventing) factor. There is the possibility that nicotinic acid, or its amide, enters into the B_2-complex, and may either be the P—P factor itself or a precursor from which it can be formed in the animal body (*Funk* and *Funk*, J. Biol. Chem. **119** (1937), Proc. XXXV; *Frost* and *Elvehjem*, ibid. **121**, 255; *Elvehjem, Madden, Strong* and *Woolley*, Am. **59**, 1767; *Chick, Macrae* and *Martin*, Biochem. J. **32** (1938), 844).

4. VITAMIN C

Anti-scorbutic Vitamin, Ascorbic Acid

The water-soluble anti-scorbutic vitamin C is widely distributed in plant products, but only few vegetable foodstuffs contain it in any great concentration. A deficiency of vitamin C in the diet causes the appearance of scurvy, a disease common in former times, particularly amongst sailors; its connection with diet was soon realised, and its cure made possible. Scurvy, the clearest example of avitaminosis, is of little importance today among adults, thanks to the knowledge of this connection with diet; but infantile scurvy (scurvy rickets, *Barlow's* disease) is still somewhat prevalent. The typical symptoms of scurvy are a characteristic state of the teeth, in which they become loose and the gums painful and spongy, frequent haemorrages in the tissues, particularly in the lower limbs, and spontaneous fractures of the bones, especially of the ribs; at the same time changes take place in the important glands, followed by a great tendency to infectious diseases. The cause in the case of adult scurvy is the lack of fresh food; in the case of infantile scurvy it is the exclusive use of pasteurised milk; in both cases the supply of vitamin C to the organism is insufficient.

The occurrence of vitamin C in lemon and orange juice is established by their curative effects, a matter of general knowledge even in 1804. The scientific investigation became possible when animals suitable for experiment were found. Guinea-pigs (also apes) are particularly sensitive to a deficiency in vitamin C, and guinea pig scurvy, with symptoms very closely similar to those of human scurvy, can be readily produced in these animals by a diet poor in vitamin C. Other animals, however, (e.g. rats and mice) are little affected by a deficiency in vitamin C, and hence it is supposed that their organism is able to convert a constituent of their food into small quantities of the vitamin.

The occurrence and stability of vitamin C under various circumstances has been explored in detail by means of animal experiments. It is found almost exclusively in fresh plant material, e.g. in green vegetables, especially in cabbages and spinach, in fruit or fruit-juice, such as lemons, oranges and tomatoes, in potatoes and in fresh milk. Researches carried out in 1932 and 1933 show that the following are particularly rich sources: the paprika fruits of *Capsicum annuum* (*Szent-Györgyi*, Nature **131**, 225), the adrenal cortex (idem, C. 1932 II 392; *v. Euler* and *Klussmann*, C. 1933 I 2836) and the thymus gland (idem, C. 1933 I 3329). It should be noticed that hens' eggs (the yolk and the white) and yeast, which is otherwise so rich in vitamins, contain no vitamin C, while the muscular tissue of animals, particularly in the fresh state, contains a small amount.

In all natural sources of vitamin C the vitamin content is diminished by boiling for a short time, especially in the presence of air; long boiling, or heating in an autoclave, completely destroys it. The vitamin is more stable in acid than in alkaline solution. When kept for some time at ordinary temperatures it gradually disappears, hence preserved pasteurised and dried foodstuffs which have been kept usually contain no vitamin.

The most typical reaction of vitamin C is its reducing power towards metallic salt solutions (Ag and Cu salts; *Zilva*, Biochem. J. **18** (1924), 182, 632), $KMnO_4$-solution, iodine solution, and particularly towards organic dyestuffs, such as methylene blue, and especially 2:6-dichlorophenol-indophenol (*Tillmans, Hirsch* and *Siebert*, C. 1932 I 1924; *Tillmans* and *Hirsch*, Biochem. Z. **250** (1933), 312; N. **21** (1933), 314). This reducing action can be applied to a quantitative volumetric estimation of vitamin C (*Schlemmer, Bleyer* and *Cahnmann*, Biochem. Z. **254**, 187); it also indicates, together with numerous tissue experiments (*v. Euler, Myrbäck* and *Larsson*, Z. physiol. Chem. **217**, 1; *v. Euler*, N. **21** (1933), 236), that vitamin C takes part in the oxidation-reduction processes of the organism.

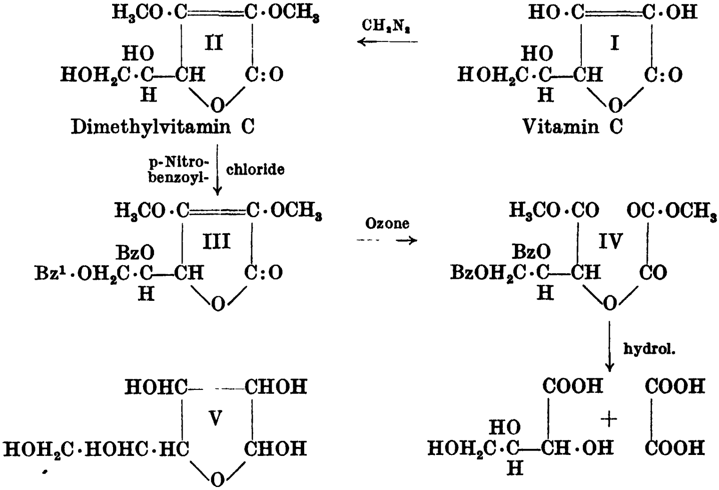
Isolation of vitamin C.— Many attempts were made to isolate the vitamin from lemon or orange juice, the process being followed by guinea pig experiments. These led, however, only to preparations rich in the vitamin, and not to a crystalline compound. With increasing concentration the reducing action and the enol reaction (with $FeCl_3$) became stronger, showing that both these properties belong to the vitamin. In the meantime, *Szent-Györgyi* found a better source for its preparation, as a result of an observation of *v. Euler*; this was the adrenal cortex. From this a substance was isolated (*Szent-Györgyi*, Biochem. J. **22** (1928), 1387) with the formula $C_6H_8O_6$, which was later recognised as the anti-scorbutic vitamin (ascorbic acid) (idem, C. 1932 II 392; *v. Euler* and *Klussmann*, C. 1933 I 2836). Later a still better source was found in the paprika: 10 litres of the juice expressed from fresh ripe fruits yield 6·5 g. of ascorbic acid (*Svirbely* and *Szent-Györgyi*, Biochem. J. **27** (1933), 279).

Vitamin C (*ascorbic acid*), $C_6H_8O_6$, m.p. 189° (from dioxan m.p. 192°), $[\alpha]_D + 48°$ (methanol), absorption maximum, 245 mμ. Na salt, $[\alpha]_D + 102–105°$, absorption maximum, 265 mμ; diphenyl-osazone m.p. 210°. Ascorbic acid is readily soluble in water and alcohol and insoluble in light petroleum; it shows the reducing action described above; it gives a strong enol reaction with $FeCl_3$, and a deep-yellow colour with tetranitromethane; it is rapidly destroyed in alkaline solution by atmospheric oxidation and oxidising agents. Derivatives: dimethyl ether, m.p. 63°, $[\alpha]_D + 38°$, from vitamin C and diazomethane (*Micheel* and *Kraft*, Z. physiol. Chem. **216**, 236); di-*p*-nitrobenzoyl dimethyl ester, m.p. 172°, $[\alpha]_D - 78·8°$. The mono-acetone compound, m.p. 222° (*v. Vargha*, Nature **130** (1932), 847), has little activity in animal experiments; elimination of the acetone re-forms the active ascorbic acid. Triphenyl-methyl derivative, m.p. 130° (dec.) (idem, Nature **131** (1933), 363).

The constitution of ascorbic acid. The experiments summarised below upon which the constitution is based were carried out by *Micheel* and *Kraft* (Z. physiol. Chem. **215**, 215; **216**, 233), and by *Hirst* and his co-workers (J. **1933**, 1270). The first constitutional formula proposed by *Micheel* and *Kraft* was revised shortly afterwards by *Hirst* (loc. cit.; Nature **131** (1933), 402; Chem. and Ind. **52** (1933), 221), and accepted by *Micheel* (Z. physiol.

Chem. **218**, 280) (see also the work of *Karrer*, *Salomon*, *Schöpp* and *Morf*, Helv. **16**, 181; Biochem. Z. **258** (1933), 4).

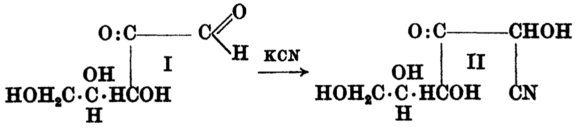
Ascorbic acid (I), an enolic lactone, is converted by diazomethane into the dimethyl ether (II), which has no reducing action. Two oxygen atoms must therefore be present as two enol groups; two further oxygen atoms can be shown to be alcoholic hydroxyls by esterification with p-nitro-benzoic acid (III). One of the alcoholic groups is primary, since it forms a triphenylmethyl ether; the two alcoholic hydroxyls must be close to one another, since an acetone compound is readily formed. The remaining two oxygen atoms are in a lactone group, which is opened by the action of dilute caustic soda on the vitamin or its dimethyl ether. The products obtained by the ozonolysis of di-p-nitrobenzoyl-dimethyl-ascorbic acid showed how these constituents are combined: the first product contains the whole of the carbon skeleton as a derivative of oxalyl-*l*-threonic acid, m.p. 162° (IV), which is hydrolysed by alkali to *l*-threonic acid (phenylhydrazide m.p. 158°), oxalic acid and p-nitrobenzoic acid:



l-Threonic acid (*l*-Threose see vol. I)

The formula of ascorbic acid (I) shows clearly its great similarity to the 1:4-oxide form of a hexose (V). Because of this relationship, it was soon found possible to synthesise natural ascorbic acid from a sugar derivative of suitable spatial configuration (*Haworth*, Chem. and Ind. **52** (1933), 482; *Haworth* and *Hirst*, ibid. 645; *Reichstein*, *Grüssner* and *Oppenauer*, Nature **132** (1933), 280; *Ault*, *Baird*, *Carrington*, *Haworth*, *Herbert*, *Hirst*, *Percival*, *Smith* and *Stacey*, J. **1933**, 1419; *Reichstein*, *Grüssner* and *Oppenauer*, Helv. **17**, 510).

When *l*-xylosone (I) is treated with KCN, it gives (II), which is very readily converted by 8% HCl into pseudo-ascorbic acid (III), and then into natural *l*-ascorbic acid (IV):



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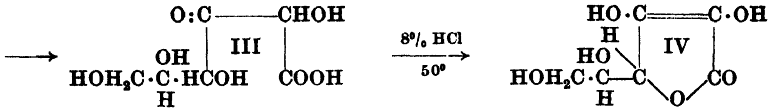
[1] Bz = $NO_2 \cdot C_6H_4 \cdot CO$.



Stereoisomers of ascorbic acid have been obtained in a similar way; *d*-xylosone gives *d*-ascorbic acid, m.p. 187–189°, $[\alpha]_D - 48^\circ$ (methanol) (*Reichstein, Grüssner* and *Oppenauer*, Helv. **16**, 561).

For the synthesis of isomers of ascorbic acid from 2-keto-gluconic acid, see ***Maurer*** and *Schiedt*, Ber. **66**, 1054. A series of isomers and homologues of ascorbic acid have been prepared by *Baird, Haworth, Herbert, Hirst, Smith* and *Stacey* (J. **1934**, 62–67), starting from *d*-glucosone, arabinosone and galactosone.

VIII. HORMONES

The term hormone means a chemical substance which is characterised by a specific physiological activity, is produced in the normal organism by certain organs and passed directly from these into the blood stream. As the tissues which produce the hormones secrete them not to the exterior, but to the interior of the organism, they are known as glands with internal secretions, or "endocrine glands", the corresponding hormone being known as an "increte" (*Roux*). The names "hormone glands" and hormones, i.e. stimulating substances (ὁρμᾶν = to incite), were introduced into the literature by Starling. The hormones usually exert their particular physiological function far away from their place of origin; hence hormones have also been called "chemical messengers", by means of which a "chemical correlation" of the organs is attained and complete collaboration guaranteed.

The investigation of hormones began in biology and medicine: the question of the functions of a particular organ was attacked by the study of the "deficiency phenomena" which appeared in the living animal after exstirpation of that organ, and which could be made to vanish by administering the corresponding glandular extract. These experiments showed that chemical compounds of importance for vital processes are produced in these organs, and that they serve as regulators of the normal processes of development, growth and metabolism. At this stage, biology set chemistry the problem of obtaining these substances in the pure state and determining their constitutions.

Hormones are normally present in nature only in exceedingly small concentrations, since their physiological action is often exerted by the minutest quantities. For the isolation of a hormone, therefore, it is essential to have a convenient source of the natural starting material, and to be able to establish the presence and concentration of the material sought by a quantitative test. It is only when these conditions are fulfilled that the investigation of the pure hormone can be attacked.

The table (p. 579) summarises the more important hormones known at present, together with their sites of formation.

A. THE HORMONE OF THE SUPRARENAL GLAND AND OF CHROMAFFIN TISSUES: ADRENALIN (suprarenin, epinephrin)

Physiology.—The adrenalin produced by the suprarenal gland is (a) a stimulant for the sympathetic system, causing a strengthening of the heart-beat and an increase in the frequency; it contracts the blood-vessels, and hence raises the blood-pressure; stomach and intestinal peristalsis are checked by adrenalin, while the contraction of the pregnant uterus is aided; by stimulating the scalp muscles it causes the hair to stand on end; after administration of adrenalin there is enlargement of the pupils, the eyelids are held open, and the eyes protrude; adrenalin increases the secretions from the lachrymatory, salivary and perspiration glands. (b) Adrenalin influences the formation of the blood: it causes an increase in the content of red and white blood corpuscles. (c) Adrenalin influences the sugar metabolism; it raises the blood sugar (hyperglycaemia) with consequent excretion of sugar in the urine (glucosuria).

The more important hormones

Site of formation (gland)	Hormone	
	Prepared pure and characterised	Investigated only in crude extracts
Adrenal gland and chromaffin-tissue	*Adrenalin* $C_9H_{13}O_3N$	
Adrenal cortex	*Corticosterone,* $C_{21}H\ _{0}O_4$	
Thyroid	*Thyroxin* $C_{15}H_{11}O_4NI_4$	
Pancreas	*Insulin* $[C_{45}H_{69}O_{14}N_{11}S]x$	
Ovary	a) *Oestrone* $C_{18}H_{22}O_2$, etc. b) *Progesterone* $C_{21}H_{30}O_2$	
Testicle	*Androsterone* $C_{19}H_{30}O_2$	
Anterior pituitary		a) growth hormone b) gonadotropic hormone c) thyreotropic hormone d) adrenotropic hormone (?)
Posterior pituitary		a) *Oxytocin* b) *Vasopressin*
Median pituitary		*Intermedin*
Parathyroid		Parathormone
Thymus		Thymus-hormone
Pineal body		Epiphyse-hormone
Intestinal mucus		*Secretin*

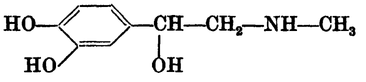
Also: a) Heart and circulatory hormone: callicrein.
b) Plant hormones: auxins.

Occurrence and distribution. — Like all the hormones, adrenalin is not peculiar to any one species; it can be isolated from the suprarenals of almost all classes of vertebrates, and in all probability also occurs in annelids and molluscs. The adrenalin content of the suprarenals varies, but it is quite certain that under certain stimuli the hormone is produced in increased quantity and passed out into the blood stream. There is a reciprocal relationship between the adrenalin delivered and the body function: the increased supply of hormone influences the functions of the body so that they can satisfy the increased demands placed upon them.

Test. — Tissue containing adrenalin is distinguished by a green colouration with ferric chloride and by a dark brown colour reaction with potassium bichromate (hence the name "chromaffin tissue") (*Vulpian*, 1856; *Henle*, 1865). It was later established that the physiological action of suprarenal extracts and the intensity of these colour reactions run parallel, so this furnished a simple colorimetric method for estimating adrenalin, and made the isolation of the pure substance much easier.

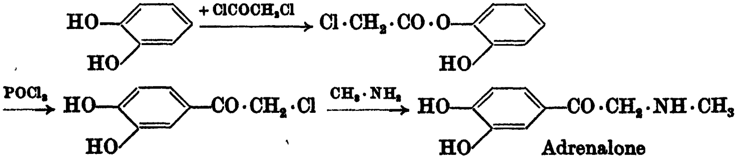
Isolation. — The isolation of adrenalin in a chemically pure, crystalline form was first achieved independently by *Aldrich* and by *Takamine* in 1901 (Am. J. Physiol. 5, 457; 7, 359; J. Physiol. 27, XXIX). Today the preparation is simple: 118 kg. of suprarenals yield approx. 125 g. of pure adrenalin. The finely-divided tissue is extracted with dilute acetic acid, the concentrated filtrate is treated with alcohol, decanted and evaporated once more; ammonia is then added in the absence of air, when the base crystallises out; it is purified by recrystallisation (*Pauly*, Ber. 37, 1388).

Properties and constitution. — **Adrenalin,** m.p. 216°, has both basic and acid properties; it is soluble in water to the extent of 1:10,000, and almost insoluble in organic solvents; with acids it forms water-soluble salts. It is a strong reducing agent and is readily oxidised. The molecular formula is $C_9H_{13}O_3N$; the nitrogen atom is eliminated as methylamine on boiling with HI, showing the presence of the group CH_3NH-; one of the three oxygen atoms is in a secondary alcohol group, and the remaining two are acidic hydroxyl groups which are easily methylated. Fusion with alkali yields pyrocatechol and pyrocatechol-p-carboxylic acid. These results show that adrenalin has the constitutional formula



(*v. Fürth*, Z. physiol. Chem. 24, 142; 26, 15; 29, 105; Mo. 24, 261; *Abel*, J. Pharmacol. 3, 219; *Friedmann*, Beitr. chem.-physiol. Path. 1, 242; 8, 95).

This structure was confirmed in 1904 by the complete synthesis of adrenalin by the following method (*Stolz*, Ber. 37, 4149; *Dakin*, J. Physiol. 32, XXXIV):



Adrenalone, which is already similar to adrenalin in its pharmacological action, is converted into adrenalin by reduction with aluminium amalgam. The synthetic product is racemic, while the natural product is laevorotatory; the racemate was resolved by means of the tartrates, which differ in their solubilities in methyl alcohol. The physiological activity of the *l*-form is 12—15 times as great as that of the *d*-form (*Flacher*, Z. physiol. Chem. 58, 189; *Abderhalden* and collaborators, ibid. 59, 22, 129; 61, 119; 62, 404; Pflüger's Archiv **196**, 608; **210**, 462; **212**, 523).

B. THE HORMONE OF THE ADRENAL CORTEX: CORTIN

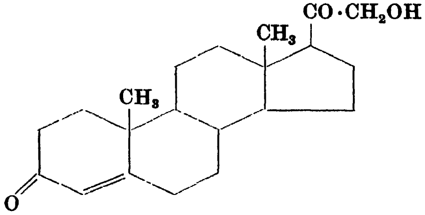
(*Interrenin*)

Physiology. — The adrenal cortex is an organ necessary to life, its complete removal promptly leading to death, after the following symptoms: muscular weakness, muscular paralysis, decrease in the frequency of respiration and thickening of the blood. Daily administration of cortical extract enables animals (cats, dogs) which have no cortex to be kept alive without showing any of these symptoms; if the administration of the extracts (subcutaneously, intraperitoneally or intravenously) is interrupted, the symptons reappear and the death of the animal follows (*Hartmann*, 1928; *Swingle* and *Pfiffner*, 1932 — Medicine, vol. XI, no. 4). The function of cortin appears to be the regulation and maintenance of a normal quantity of fluid in the vascular system. In the absence of the hormone, the normal blood volume decreases, probably because too much liquid passes through the walls. As a consequence of this decrease in volume lack of cortin produces a fall in blood pressure, thickening of the blood, an increase in the number of red blood corpuscles, an increase in the frequency of the heart-beats, decreased kidney action and an increased urea content in the blood. Administration of cortin immediately causes the blood to become thinner, and the secondary deficiency phenomena vanish (*Swingle*, Science 77, 58).

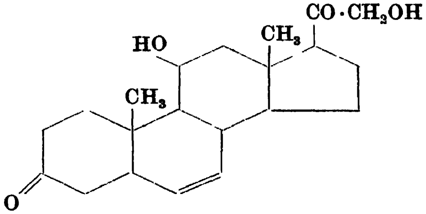
Test. — The adrenalectomised dog can be used for the quantitative estimation of cortin. The "dog-unit" is defined as the smallest daily dose of cortin per kg. of dog necessary to keep the animal in a physiologically normal condition for a period of 7—10 days. A quantitative criterion is given by the nitrogen content of the blood, which by its increase above the normal is the first sign of a deficiency of cortin.

Preparation of active extracts, isolation of cortin and its properties. — For the preparation of an active extract, the adrenal cortex is extracted with methyl alcohol, and the fraction of the extract soluble in benzene and acetone is mixed with 70% alcohol and light petroleum; the alcoholic phase is filtered through permutite to remove the adrenalin (p. 579), and transferred to aqueous solution. In this way, 40 g. of cortex yield 40—80 dog-units in aqueous solution (*Swingle* and *Pfiffner*, Medicine **11**, 371).

From the active extract a series of crystalline compounds have been isolated, the majority of which were shown to be inactive, although it was possible to establish the structure of some of them (*Kendall* and co-workers, J. Biol. Chem. **114** (1936), 613; *Winterstein* and *Pfiffner*, ibid. **111** (1935), 599; **114** (1936), lxxx; *Reichstein* and co-workers, Helv. **19**, 26, 223, 401, 979, 1107; **20**, 217). One of Reichstein's compounds, however, which was later obtained by Kendall, was found to be highly active and the requisite daily dose for an adrenalectomised rat was only 0·5—1·0 mg. This compound has been called **corticosterone**; its composition is given by $C_{21}H_{30}O_4$; m.p. 180—182°, $[\alpha]_D^{15} = + 223°$ (in alcohol) (*Reichstein*, Nature **139** (1937), 26; Proc. K. Acad. Wetensch. Amsterdam **39** (1936), 1218). It is related in structure to the sex hormones which are discussed later, and the clue to its constitution was given by the observation that 21-hydroxy-progesterone, m.p. 136—138°, which can be prepared from stigmasterol, shows definite cortical activity. This is the first substance of such activity to be prepared from inactive material (*Steiger* and *Reichstein*, Nature **139** (1937), 925). Further work has shown that corticosterone differs from this compound in containing an extra hydroxyl group, which is almost certainly in the 11-position (*Reichstein*, Helv. **20**, 953; *Mason*, *Hoehn*, *McKenzie* and *Kendall*, J. Biol. Chem. **120** (1937), 719).



21-Hydroxy-progesterone



Corticosterone

C. THE HORMONE OF THE THYROID GLAND: THYROXIN

Physiology. — The thyroid gland is of profound importance for normal physical development, for growth and metabolism, and for the formation of the mental disposition of an organism. Removal of the thyroid leads to athyreosis; this can be recognized by symptoms which are described as those of myxoedema and cretinism: puffy appearance of the skin, dryness of the epidermis, loss of the hair, nails and teeth, physical and mental slowness increasing up to dementia; in the young organism the growth is markedly retarded and sexual development ceases. Accompanying these outer symptoms are a decrease in the metabolism, a slowing of the action of the heart and loss of regenerative ability. — In men and animals the symptoms of athyreosis can be eliminated by implanting thyroid tissue under the skin, in the spleen or in the peritoneum. Excessive action of the thyroid gland leads to the symptoms of exophthalmic goitre (Basedow's disease), a rise in the basal metabolism, wasting, mental activity, a strong reflex, distended pupils and protruding eyes. — In 1895, *Baumann* discovered that iodine is a normal constituent of the thyroid gland in a quantity far exceeding that in any other organ (Z. physiol. Chem. **21**, 319); he was the first to prove that this iodine is present in an organic compound and is connected with the physiological activity of the thyroid gland.

Test. — Because of its iodine content the hormone of the thyroid gland can be detected by a simple chemical reaction: quantitative determination of the iodine furnishes a simple method for estimating the thyroid hormone. For biological tests, see below.

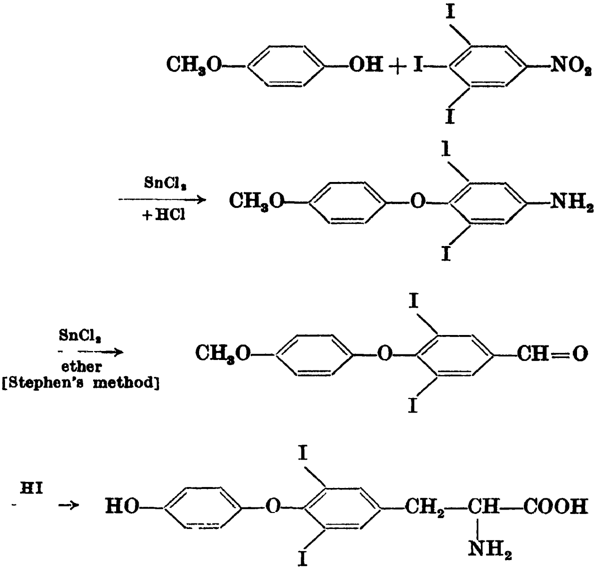
Isolation. — *Oswald* (1896—1910) extracted thyroid glands with physiological saline and precipitated a protein fraction from the extract by adding saturated ammonium sulphate; this protein fraction contained thyreoglobulin, the hormone of the thyroid gland (Z. physiol. Chem. **27**, 14). In 1919 *Kendall* hydrolysed the thyreoglobulin with alkali and obtained a crystalline substance, which had all the activity of the thyroid gland and was named thyroxin (J. Biol. Chem. **20**, 501). The preparation of thyroxin was considerably improved by *Harington* (1926), to whom we owe the determination of the constitution and the synthesis of the hormone (*Harington*, Biochem. J. **20** (1926), 300; *Harington* and *Barger*, ibid. **21** (1927), 169).

For the preparation of thyroxin from the thyroid gland, careful alkaline hydrolysis of the tissue is used, firstly with 10% baryta and then with 2% caustic soda. Impurities can be salted out from the alkaline solution with sodium sulphate, while the hormone remains in solution; it is precipitated by acidifying with dilute HCl. The product can be purified to a considerable extent by repeating the process with slight variations. 1 kg. of dried thyroid glands yield about 1 g. of pure crystalline thyroxin.

Determination of the constitution and synthesis. — Thyroxin has the composition $C_{15}H_{11}O_4NI_4$; careful catalytic hydrogenation converts it into desiodo-thyroxin (thyronin), $C_{15}H_{15}O_4N$, which behaves both like an α-amino-acid and a phenol. Fusion of thyronin with alkali yields *p*-hydroxy-benzoic acid, hydroquinone, oxalic acid and ammonia. On the basis of these results, thyroxin was given the constitution (I), which was proved by the partial synthesis of several degradation products and finally by the complete synthesis of thyroxin itself. The method of synthesis is shown in the formulae below (pp. 584, 585).

The synthetic product is identical in all respects with the preparation from thyroid gland, and possesses all the typical pharmacological properties of thyroid gland (*Harington* and *Barger*, loc. cit.; *Lyon*, ibid. **21** (1927), 181; *Gaddum*, J. Physiol. **64**, 246).

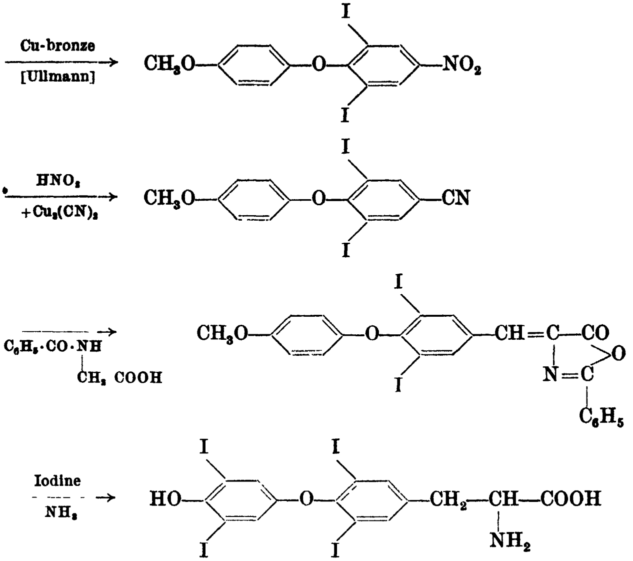
Properties. — Thyroxin is insoluble in water, and only slightly soluble in organic solvents. With alkali it forms salts soluble in water, while it is only slightly soluble in dilute acids. Its iodine content is 65·3%. Thyroxin decomposes at 231—233° with evolution of iodine, and has a typical absorption spectrum in the ultraviolet with a maximum at 325 mμ (*Abderhalden* and *Rossner*, Z. physiol. Chem. **169**, 223). Thyroxin isolated from the gland is optically inactive, like the synthetic product. *l*-Thyroxin can be isolated



from the thyroid gland by using proteolytic enzymes. The synthetic product has been resolved into its optical antimers; *l*-thyroxin has a physiological action about three times as great as that of *d*-thyroxin (*Harington*, Biochem. J. **22** (1928), 1429; *Harington* and *Salter*, ibid. **24** (1930), 456; *Gaddum*, J. Physiol. **68**, 383).

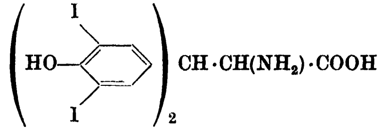
Pharmacological properties of Thyroxin. — Thyroxin causes an increase in the basal metabolism and in the metabolism of protein and fats; administration of thyroxin causes an increase in the metabolism of 15—20%, with considerable wasting and loss of weight of the test animal. Thyroxin increases the excitability of the vagus and hence causes a mobilisation of adrenalin by stimulation of the sympathetic and parasympathetic nervous systems; this gives rise to the adrenalin effect (p. 579) on the sugar metabolism and the cardiac and vascular systems. Thyroxin accelerates the metamorphosis of tadpoles (*Gudernatsch*), which shows the significance of this hormone in the differentiation of tissues and organs; tadpoles from which the thyroid gland has been removed never undergo metamorphosis. Thyroxin raises the resistance of white mice to poisoning by acetonitrile, and this specific action can be used for the biological estimation of thyroxin (*Reid-Hunt* reaction); the acceleration of metamorphosis has also been used (*Zih*, Pflügers Arch. **214**, 449; *Cameron* and *Carmichael*, J. Biol. Chem. **45**, 69; Arch. Entw.-mechan. **35**, 457; **41**, 47; Amer. J. Physiol. **63**, 257).

The physiological action of thyroxin is not an iodine effect, but a specific property of the molecule. Substances with the thyroxin structure, but with different halogen in place of iodine, have a physiological action qualitatively similar to that of thyroxin.



I. Thyroxin

Thyronin, however, has no physiological action, and the isomer of thyroxin of the formula



is likewise inactive (*Harington* and *McCartney*, J. **1929**, 892). For dibromo-, dichloro- and diiodo-thyronin, and tetrabromo- and tetrachloro-thyronin, see *Schuegraf*, Helv. **12**, 405; *Abderhalden* and *Wertheimer*, Z. exper. Med. **63**, 557; **68**, 563.

D. THE HORMONE OF THE PANCREAS: INSULIN

Physiology. — Removal of the pancreas causes profound disturbance in carbohydrate metabolism (*v. Mering* and *Minkowski*, 1889), and even after a few hours glucose is excreted in the urine. This glycosuria reaches its maximum after 3 days, when up to 20% of glucose is excreted, and does not disappear, even if the diet contains no sugar: it corresponds to the main symptom of ***diabetes mellitus***, a disease which arises from the fact that the liver loses its capacity for retaining glucose as glycogen. Among the secondary symptoms there are considerable increases and disturbances in the metabolism of protein and fats, which lead to wasting and to the excretion of ketones in the urine ("ketosis"). This pancreas diabetes can be cured by implanting pancreas or by administering a pancreas extract prepared in a special way (*Banting* and *Best*, 1920); it is caused by a deficiency in the hormone insulin which is produced in a certain part of the pancreas (the "islets of Langerhans").

Test. — The identification and biological standardisation of insulin is based upon its action in reducing the sugar content of the blood; in normal animals the reduction is proportional to the dose administered. The original "insulin unit" was that quantity of substance which, when injected into a rabbit weighing 2 kg., kept without food for 24 hours, reduced the blood sugar to one half (i.e. from 0·09 % to 0·045 %) in 4 hours. Insulin is estimated today by comparison with the activity of an international standard.

Isolation of insulin. — According to *Collip*, insulin can be extracted from pancreas with acidified alcohol. The crude extract is purified by removing the fats and lipoids and the protein substances which accompany the hormone; fats and lipoids are separated by extraction of the alcohol-soluble fraction with ether, which does not dissolve insulin; the separation of inactive proteins is carried out by salting out in aqueous solution, precipitation at the isoelectric point of insulin (pH 5—5·4), by the addition of picric acid or potassium lactate, or by the adsorption of the insulin upon benzoic acid or charcoal followed by elution (Erg. Physiologie **23**, 213; *Crowdle* and *Sherwin*, J. Biol. Chem. **55**, XL; **57**, 709; *Piper*, *Allen* and *Murlin*, ibid. **58**, 321; **60**, 31; *Scott*, ibid. **65**, 601; **81**, 167; Am. J. Physiol. **64**, 348; **100**, 285; J. Pharmacol. **25**, 423; **31**, 65; Biochem. J. **17**, 376; *Dudley* and *Starling*, ibid. **18** (1924), 147; *Langecker* and *Wiechowski*, Klin. Wochschr. **1925**, 1339).

In 1925, *Abel* succeeded in preparing insulin in a crystalline form (J. Pharmacol. **31**, 65; **32**, 367; **36**, 115). Brucine was added to a purified acetic acid solution of purified insulin, and addition of pyridine brought down an inactive precipitate, which could be centrifuged off, and a further one was produced by the addition of ammonia; crystalline insulin separated from an ammoniacal solution at pH 5·5 on standing. The starting materials for its preparation were the pancreas of cattle, horses, pigs, and sheep. Crystallisation is much easier in the presence of small amounts of divalent metallic ions, such as Zn, Ni, Co and Cd, and their presence is very probably essential (*Scott*, Biochem. J. **28** (1934), 1592); the metal is chemically combined with the insulin in the crystal.

Properties of crystalline insulin. — Insulin is laevorotatory; its density is 1·315, and 1 mg. contains 25 biological units. Its chemical investigation has been carried out chiefly by *Abel*, *Jensen* and *Freudenberg*: crystalline insulin contains approximately 53 % C, 6·8 % H, 21·7 % O, 15·4 % N and 3·14 % S; the ultracentrifuge shows that its molecular weight is 35,100 (*Svedberg* and *Sjögren*, Am. **53**, 2657), a result which agrees with the X-ray crystallographic data (*Crowfoot*, Proc. Roy. Soc. **164** A (1938), 580). It is a protein and is decomposed by digestion with trypsin or by acid hydrolysis into amino-acids, of which the following have been isolated: cystine, tyrosine, arginine, valine, lysine, leucine, histidine and glutamic acid. Tryptophan has not been found. The isoelectric point of insulin is at pH 5—5·4; it is stable to heat, and hence can be sterilised in aqueous solution. It is considerably more sensitive to alkalis than to acids (*Jensen* and *Wintersteiner*, J. Biol. Chem. **97**, 93; **98**, 281; *Jensen* and *Evans*, Z. physiol. Chem. **209**, 134; Science **1932**, 14).

The physiological activity of insulin is evidently bound up with the protein structure, and no success has attended the efforts which have be made to separate a protein-free "prosthetic group" from the molecule. According to *Freudenberg*, the problem of determining the structure is therefore "to explore for the active group inside the large protein molecule". This has been undertaken with the aid of chemical, physical and enzymatic methods, and has led to the conclusion that the active group represents about 3% of the whole molecule and is united to the rest by links of the same kind as those which hold the whole protein molecule together.

Methods of investigation of the active group of insulin (*Freudenberg* and *Dirscherl*, Z. physiol. Chem. **180**, 212; *Freudenberg, Dirscherl* and *Eyer*, ibid. **187**, 89; **202**, 128; *Freudenberg, Dirscherl, Eichel* and *Weiss*, ibid. 159; *Freudenberg* and *Dirscherl*, ibid. 192; *Freudenberg* ibid. **204**, 233; *Freudenberg* and *Eyer*, ibid. **213**, 226; *Freudenberg, Weiss* and *Eichel*, ibid. 248):

(a) *Chemical methods.* When insulin reacts with formaldehyde, its activity disappears, and about 2% of CH_2O is taken up. Since an equal quantity of formaldehyde is taken up by inactive insulin, the amount reacting with the active group must be very small, i.e. the active group is exceedingly small. The aldehyde is eliminated again by heating with dilute HCl, and the activity is partly regained. The formaldehyde may have reacted with an NH_2 or an $NH <$ group. — Acetylation of insulin gives an acetyl derivative which has lost almost all activity; under mild conditions the acetyl group can be hydrolysed off once more, giving a physiologically active substance different from the original material. Comparison experiments on the ease of hydrolysis show that the $\cdot COCH_3$ which has entered the active group can only be attached to OH or $NH <$ and not to NH_2. — The action of N/30 alkali at 34° inactivates insulin in 3—4 hours, with evolution of ammonia; this ceases when the inactivation is complete, and runs parallel with the fall in activity: 0·16% of NH_3 is eliminated, which suggests that four molecules of ammonia are lost from each molecule of insulin. — Reduction of insulin with Na amalgam makes it inactive, and one half as much ammonia is eliminated as in alkaline hydrolysis; subsequent treatment with alkali leads to the elimination of the second half of the ammonia. From this it follows that alkali eliminates four mol. of NH_3 from insulin, and that two of the groups giving ammonia are sensitive to reduction. — Insulin can be esterified with alcohol and acid or with diazomethane; the ester is inactive, but the activity returns on hydrolysis; hence the active group contains a COOH group. — Perbenzoic acid inactivates insulin, i.e. the active group is attacked by perbenzoic acid; from the known molecular weight, it has been shown that the active group reacts with two molecules of perbenzoic acid.

(b) *Enzymatic methods.* Trypsin, pepsin, papain and cathepsin inactivate insulin by hydrolysing the protein chain. Digestion with papain can be carried out so that inactivation takes place before fission, and this must mean that the nitrogenous group which is sensitive to alkali and reduction is also attacked in this process. The active group appears therefore from the enzymatic experiments to behave like a protein, and for it to be active, it must form an integral part of the protein structure.

(c) *Optical methods.* Insulin has a typical absorption maximum at 280 mμ, which from its position and intensity may be due to tyrosine and cystine. By observing the changes in absorption caused by treatment with chemical reagents it has been shown that an alteration in the absorption means a decrease in the physiological activity. — The decrease in activity caused by the action of alkali or reducing agents is accompanied by a marked change in the optical rotation; from this it has been concluded that the active group contains a centre of asymmetry which is easily influenced; it is possible that tyrosine and cystine are components in the structure of this group.

Constitution of insulin.—The conclusions drawn from the experiments described can be summarised in the following picture of the constitution of insulin. It consists of an active group and a protein component which forms by far the greater part of the molecule, but is of minor importance for the physiological action. It is not possible to separate the active group, which is structurally part of the protein, and is not a group of a type different from the protein component. The active group consists of an arrangement of amino-acids, or derivatives of these, arranged very much as in a protein. — The active group represents 3% of the molecule at the most, and it is not known of which amino-acids it is composed, but on spectroscopic grounds tyrosine and cystine are possible. The active group contains a grouping which can eliminate four NH_3, and may contain sensitive $CONH_2$ or $>C:NH$-groups; one of these groups is particularly labile, and practically all reagents which deactivate insulin attack this group. The following groups can be assumed, with some probability, to be present in the active group: $>NH$, OH, COOH and one asymmetric C-atom.

E. THE SEX HORMONES

In the higher organisms the sexual changes which take place at puberty are connected with the endocrine activity of the sexual glands. Castration of the young organism of either sex leads to permanent immaturity and the secondary sex characteristics do not appear; castration of an organism after puberty results in atrophy of the genital organs, disappearance of sexual activity and the loss of many of the exterior sex characteristics. The more obvious deficiency symptoms which occur after castration can be removed in the male organism by administering testicular extracts, and in the female organism by ovarian extracts. Hence it follows that in both sexes specific hormones are produced in the sex glands, the physiological functions of which are to cause the growth and development of the sexual organs, to regulate their functions, and to produce the secondary sexual characteristics.

1) THE HORMONES OF THE MALE SEXUAL GLANDS: ANDROSTERONE

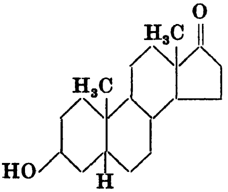
Physiology. — The male sex hormone (testicular hormone), formed in the male sex-glands (testicles), is distinguished by the following physiological functions: it causes the formation of the male genital tract and its accessories, the growth of the vas deferens, Cowper's glands, the prostate, the seminal vesicles and the penis; it influences the functions of the genital organs, the secretions of the subsidiary glands, and the life and motility of the sperms. Under its stimulus the secondary male sex characteristics are formed, e.g. the breeding dress of the carp, the comb, wattles and spurs of the cock (*Berthold*, *Steinach*, *Koch*, *Moore*, *Funk*, *Loewe*, etc.).

Test. — Identification and quantitative estimation of the testicular hormone is best carried out by its effect upon the development of the seminal vesicles (vesicular glands) of castrated male rodents ("vesicular gland test" of *Loewe* and *Moore*), or on the growth of the undeveloped comb of a capon ("comb test" of *Koch*). One comb-unit of the hormone, for example, is defined as that quantity of substance which, administered on two successive days to each of three capons, causes during the third and fourth days an average increase of 20% in the area of the combs. The area of the comb is measured planimetrically from a shadowgraph of the comb (*Butenandt* and *Tscherning*, Erg. d. Physiol. **35** (1931), 301).

Occurrence. — The male sexual hormone has been found by this test to be present in the blood of mammals as well as in the testes and epididymis, and is excreted in human male urine normally in small amounts; e.g. 5—6 comb-units per litre (*Funk*, *Harrow* and *Lejma*, Am. J. Physiol. **92**, 440; *Loewe*, *Rothschild*, *Rautenbusch* and *Voss*, Klin. Wochschr. **1930**, 1407; Biochem. Z. **221** (1930), 461). This discovery showed that male urine was a good starting material for the chemical investigation of the testicular hormone.

Isolation. — With the aid of the comb test the testicular hormone was first prepared in a chemically pure and crystalline form from male urine (*Butenandt* and *Tscherning*, Erg. d. Physiol. **35** (1931), 301). Acidified urine was extracted with $CHCl_3$; 92% of the soluble fraction was removed by shaking with aqueous alkali, and a further 35% of the remaining neutral product by distillation in steam. The non-volatile residue contains the hormone and was hydrolysed with alkali and acid, the hormone remaining in the unsaponifiable neutral portion; it was further concentrated by distribution between benzene, petroleum ether and 60% alcohol (it passes into the latter), and was then separated as its oxime by the addition of hydroxylamine. The oxime, m.p. 215°, is converted by dilute acids into the crystalline hormone, which is called **androsterone**; it has m.p. 178°, and contains one comb-unit (according to the above definition) in 150—200 γ; $\alpha_D^{20°} = +93{\cdot}5°$. 100 litres of urine contain 100 mg. of androsterone, of which 25 mg. can be isolated in the pure state.

Constitution. — The composition of androsterone corresponds to the formula $C_{19}H_{30}O_2$; it contains one hydroxyl group (acetate m.p. 161°; propionate m.p. 145°) and one carbonyl group (oxime m.p. 215°). Androsterone is saturated and hence contains four hydrogenated rings in the molecule. Reduction of the carbonyl group to an alcohol converts androsterone into a dihydro-derivative, m.p. 219°; this diol has a considerably stronger effect upon the comb than the ketone. — Male urine which has been hydrolysed with HCl contains, in addition to androsterone, an unsaturated chloroketone, $C_{19}H_{27}OCl$, m.p. 157°, which is physiologically inactive; it shows its relationship to the sterols (p. 548) by intense sterol colour reactions; semicarbazone m.p. 275°. It can be reduced catalytically to the dihydro-chloroketone, $C_{19}H_{29}OCl$, m.p. 173°, which is converted into androsterone acetate by treatment with potassium acetate at 170—180°. This preparation of androsterone from physiologically inactive material proves its individuality and shows that the physiological activity is a property of the molecule. This experiment also indicates that androsterone has the same carbon skeleton as the sterols, and from its chemical behaviour, *Butenandt* (N. **21** (1933), 49), who had only 25 mg. to work with, suggested that it had the following structure:



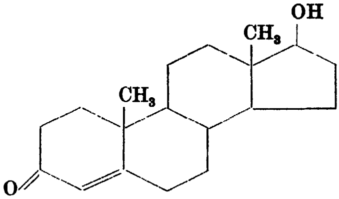
Such a molecule can exist in a large number of stereo-isomeric forms, but the most probable configurations for most of the molecule are those which are common to the sterols and the bile acids. This assumption reduces the possibilities to the four which differ in the arrangement at positions 3 and 5, i.e. at the OH and H in the above formula. *Ruzicka* and his co-workers (Helv. **17**, 1389, 1395, 1407) found that dihydrocholesteryl acetate can be oxidised to a ketone of the above formula, but that the product was not identical with the hormone. They then completed the series and prepared the other three probable isomers; the one obtained from epi-dihydrocholesterol proved to be completely identical with androsterone, and hence the structure suggested by *Butenandt* is confirmed. *Ruzicka's* work has made the hormone much more accessible than it is from natural sources, because cholesterol is a comparatively cheap starting material, and methods for its preparation from that source have been worked out (*Callow* and *Deanesly*, Biochem. J. **29** (1935), 1424; *Marker*, Am. **57**, 1755, 2358).

HCl can be eliminated from the saturated chloroketone mentioned above, $C_{19}H_{29}OCl$, m.p. 173° (the chloride of androsterone), giving the unsaturated ketone, $C_{19}H_{28}O$, m.p. 104°; hydrogenation of this yields the saturated ketone, $C_{19}H_{30}O$, m.p. 122°, which can be reduced to the saturated fundamental hydrocarbon of androsterone, androstane $C_{19}H_{32}$, m.p. 50°.

Dehydro-androsterone, $C_{19}H_{28}O_2$, m.p. 148°, can be prepared via its benzoate, m.p. 250°, by the interaction of the unsaturated chloroketone mentioned above and potassium benzoate at 180°; it is also found with androsterone in male urine; in the comb-test it has only 1/3 of the physiological activity of the saturated substance.

Testosterone, $C_{19}H_{28}O_2$, m.p. 154°, $[\alpha]_D = +109°$. Further biological tests showed that male hormone extracts obtained from urine and from testes were not identical, particularly in their effect on the growth of the seminal vesicles of the castrated rat, and pointed to the existence of another powerful hormone in the testicular extracts (see inter alia, *Freud* and *Laqueur*, Nature **135** (1935), 184).

This hormone was isolated in 1935 (*David*, *Dingemanse*, *Freud* and *Laqueur*, Z. physiol. Chem. 233, 218) and is called testosterone; it is ten times as active as androsterone in the comb test and about seven times in the rat test. Its chemical behaviour suggested the formula:



Δ^4-Androstenol-17-one-3.

This has been confirmed by its preparation from dehydro-isoandrosterone (*Butenandt* and *Hanisch*, Z. physiol. Chem. 237, 89; *Ruzicka* and *Wettstein*, Am. 57, 2011; Helv. 18, 1264). It seems probable that testosterone is the characteristic male hormone of the testes and that those excreted in the urine are transformation products. Various related substances have been prepared (*Butenandt*, *Tscherning* and *Hanisch*, Ber. 68, 2097), but testosterone remains the most potent male hormone known.

2) THE FEMALE SEX HORMONES: THE FOLLICULAR HORMONES (OESTRONE, ETC.) AND THE CORPUS LUTEUM HORMONE (PROGESTERONE)

Physiology. — The female ovary produces two sex hormones, one in the follicle, the sac containing the egg during its development and ripening, and a second in the yellow body (*corpus luteum*) which is formed from the follicle after the ripening and expulsion of the egg. The female sex hormone of the follicle (follicular hormone, oestrone, theelin) governs the growth of the female genital organs, and is a growth substance with a specific action upon the uterus, the vagina and the lacteal glands; it also causes the proliferation of the uterine mucus which takes place during the ripening of the follicle. Hence it controls part of the phenomena of oestrus and menstruation which are characteristic of the female genital system, and are shown histologically by a periodic building up and degradation of the uterine mucus (*Knauer*, *Steinach*, *Allen*, *Doisy*, etc.). — The female sex hormone formed in the corpus luteum (progesterone) has the function of reconverting the uterine mucus, proliferated by the action of the follicular hormone, into a secretory mucus (*Allen*, *Corner*, *Clauberg*).

Test. — The follicular hormone is recognised by an oestrus reaction with castrated female rodents: the subcutaneous injection of 1 mouse-unit of follicular hormone into a castrated mouse is that which causes a single oestrus cycle, the maximum of which is characterised by the occurrence of horn-like, anucleate cells in the vagina (*Allen-Doisy* test).

The *corpus luteum* hormone is tested by its action upon the proliferated uterine mucus of the immature rabbit: one rabbit-unit causes a complete transformation of the endometrium proliferated by the follicular hormone into secretory mucus (*Corner-Clauberg* test; *Clauberg*, Die weiblichen Sexualhormone, Berlin, 1933).

Distribution and occurrence. — The follicular hormone is found in the ovary, in the follicle and the follicular liquid, in the blood and urine of mammals and human beings. During pregnancy it is formed in the placenta and excreted in large quantities in the urine; a particularly rich source is the urine of pregnant mares. It occurs in all classes of animals and is found widely distributed in the plant kingdom; it has also been detected in bitumen. Androsterone is always accompanied by the follicular hormone, and in surprisingly large quantities in the testes and urine of stallions (*Störmer* and *Westphal*, Erg. d. Physiol. **35**, 318; *Zondek*, Nature **133**, 209).

The *corpus luteum* hormone is found in the gland itself and in the placenta (*Adler*, *de Fremery* and *Tausk*, Nature **133**, 293).

Isolation of the follicular hormones. — A follicular hormone was isolated in the pure crystalline state in 1929 by Doisy and by Butenandt independently (*Doisy*, *Veler* and *Thayer*, J. Biol. Chem. **86**, 499; **87**, 357; *Butenandt*, N. **17**, 879; Z. physiol. Chem. **191**, 127). The original starting material was urine of pregnancy, but later it was isolated from mares' urine, placenta and palm kernels (Erg. d. Physiol. **35**, 318; *Butenandt* and *Browne*, Z. physiol. Chem. **216**, 49; *Butenandt* and *Jacobi*, ibid. **218**, 104). In its isolation, use was made of its solubilities and of its chemical character as an unsaponifiable substance with weakly acid properties, stable towards acids, alkali and temperature.

The portion of the starting material soluble in ether is best subjected to aqueous alkaline hydrolysis by several hours' heating on the water-bath with 5% caustic potash; the alkaline solution is saturated with CO_2 and exhaustively extracted with ether; the alkali-soluble (phenolic) part of the ether extract is then distributed between 50% alcohol and high-boiling petroleum ether, and the material from the alcoholic solution is then distributed between 60% alcohol and benzene; the benzene layer, which contains most of the hormone, is finally heated for 3 hours with dilute alcoholic HCl, and the phenolic portion (soluble in alkali, insoluble in carbonate) which remains after this hydrolysis is distilled in high vacuum (0·02 mm. Hg) at 130—160°. This gives the crystalline hormone, which can be purified by recrystallisation from acetic ester and dilute alcohol.

The crystalline hormone obtained in this way is known as oestrone, the α-follicular hormone; it forms monoclinic or rhombic crystals of m.p. 259°, and has a characteristic absorption maximum at 280—285 mμ; $\alpha_D = + 8{\cdot}5^0$. It is a hydroxy-ketone, $C_{18}H_{22}O_2$: acetate m.p. 126°, benzoate m.p. 217·5°, oxime m.p. 233°, methyl ether m.p. 167° (*Butenandt*, Z. physiol. Chem. **191**, 140; *Butenandt* and *Störmer*, ibid. **208**, 129; for other methods of separation see: *Beall* and *Marrian*, Chem. and Ind. **53**, 309 T: *Beall* and *Edson*, Biochem. J. **30**, 577). It was formerly called oestrin, but this name is best reserved for the group of which oestrone and oestradiol are representatives.

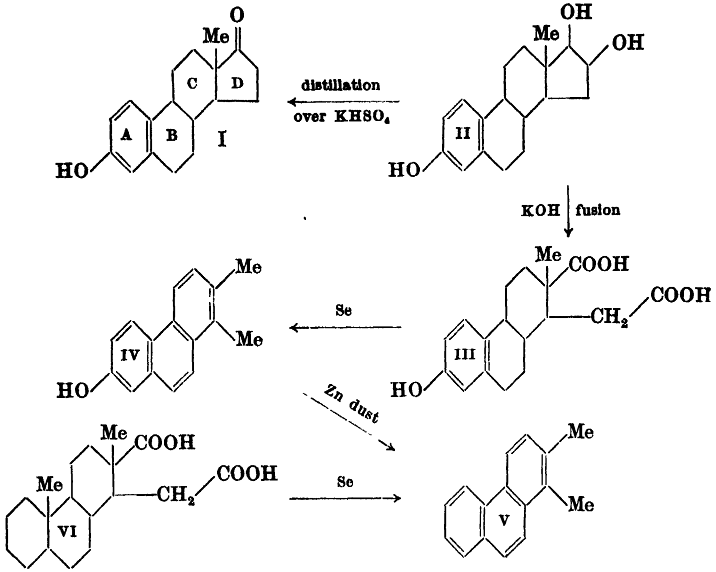
Careful investigation of the urine of pregnancy, mares' urine and placenta has shown that there are other characteristic substances besides the α-follicular hormone which exert the same physiological actions: the following table summarises several of the more closely investigated follicular hormones (*de Jongh*, *Kober* and *Laqueur*, Biochem. Z. **240**, 247; *Girard* and collaborators, C. r. **194**, 909; 1020; *Schwenk* and *Hildebrandt*, N. **20**, 658; Endocrinology, **15**, 315; *Marrian*, Biochem. J. **23**, 1090, 1233; **24**, 435, 1021; *Butenandt* and *Browne*, Z. physiol. Chem. **216**, 49; *Wintersteiner*, *Schwenk*, *Hirschmann* and *Whitman*, Am. **58**, 2652):

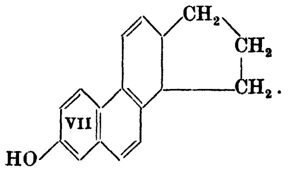
Summary of crystalline follicular hormones

Substance	Formula	M.p.	Optical rotation	Physiol. activ. per gram	Isolated from
α-Follicular hormone: oestrone	$C_{18}H_{22}O_2$	259°	$\alpha_D = +158{\cdot}5°$	8–10 Mill. MU	Urine of pregnancy and mares' urine
δ-Follicular-hormone	$C_{18}H_{20}O_2$	215–217°	$\alpha_D = -4{\cdot}7°$	4–5 Mill.MU	Mares' urine
Oestriol (theelol)	$C_{18}H_{24}O_3$	280°	$\alpha_D = +30°$	75,000 MU	Urine of pregnancy. placenta
Equilin	$C_{18}H_{20}O_2$	238–240°	$\alpha_D = +308°$	~1·5 Mill. MU	Mares' urine
Hippulin	$C_{18}H_{20}O_2$	233°	$\alpha_D = +128°$	~1·5 Mill. MU	Mares' urine
Equilenin	$C_{18}H_{18}O_2$	258–259°	$\alpha_D = +87°$	400,000 to 700,000 MU	Mares' urine

The δ-follicular hormone is a diol and is related to equilenin, and oestriol, $C_{18}H_{24}O_3$, first isolated by Marrian, is a triol: triacetate m.p. 127°, $\alpha_D = +16°$. Equilin, hippulin and equilenin are unsaturated hydroxy-ketones, the first two with four and the last with five double bonds (formula XI, p. 596).

Constitution of oestrone. — Oestrone has the constitutional formula (I) and oestriol is (II); the latter is dehydrated by distillation in a high vacuum over $KHSO_4$ to oestrone. — The formulae are based upon the following experimental results: measurements of molecular refraction and the preparation of saturated hydrogenation products show the presence of an unsaturated system of four rings with three double bonds (hexahydro-desoxo-oestrone, $C_{18}H_{29}\cdot OH$, m.p. 105°; hexahydro-oestriol, $C_{18}H_{27}(OH)_3$, m.p. 256°; hexahydro-desoxy-oestriol, $C_{18}H_{28}(OH)_2$, m.p. 153°). These bonds have an aromatic character and are indifferent towards all reagents; their conjugation gives rise to the ultraviolet absorption maximum of the hormone at 285 mμ, but they do not produce an exaltation in the molecular refraction. One hydroxyl in all the crystalline follicular hormones investigated is in the aromatic nucleus and shows phenolic properties; hence the hormones behave as weak acids (*Butenandt* and *Westphal*, Z. physiol. Chem. **223**, 147).



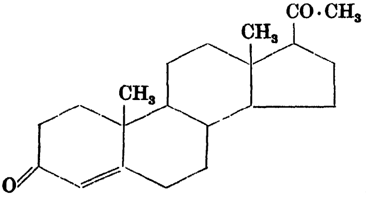


Crystallographic measurements and surface film experiments indicate that oestrone has a poly-condensed ring system, and that the functional groups are at opposite ends of the molecule and as far apart as possible (*Bernal*, Chem. and Ind. **51**, 466; *Adam* and collaborators, Biochem. J. **26**, 1233; *Danielli*, Am. **56**, 746). The nature of the ring system was confirmed by the following degradation: oestriol (II) is converted by alkali fusion into the dicarboxylic acid $(HO)C_{16}H_{19}(COOH)_2$ (III), which yields its anhydride on distillation; this makes it probable that the carboxyls are 1:5 to one another. The dicarboxylic acid (III) can be smoothly dehydrogenated by selenium to 7-hydroxy-1:2-dimethyl-phenanthrene (IV), m.p. 197°, and this by distillation with Zn dust to 1:2-dimethyl-phenanthrene (V), m.p. 140° (see also *Haworth* and *Sheldrick*, J. **1934**, 864; *Cohen*, *Cook*, *Hewett* and *Girard*, ibid. 634). In agreement with this constitutional formula, oestrone and its derivatives can be dehydrogenated under energetic conditions into cyclopentenophenanthrol (VII) and chrysene (*Butenandt*, *Weidlich* and *Thompson*, Ber. **66**, 601; *Butenandt* and *Thompson*, Ber. **67**, 140; *Cohen*, *Cook*, *Hewett* and *Girard*, J. **1934**, 653).

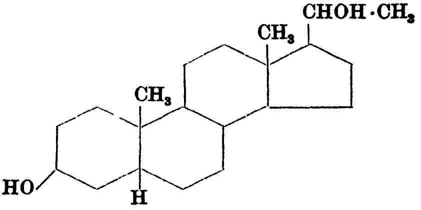
Gentle reduction of oestrone gives dihydro-oestrone (oestradiol), m.p. 170°, in which the carbonyl group is replaced by a secondary alcohol group. This change is accompanied by a marked increase in physiological activity (*Schwenk* and *Hildebrandt*, N. **20**, 658; **21**, 177). This compound has been isolated in very small amounts from the ovaries of pigs (*MacCorquadale*, *Thayer* and *Doisy*, J. Biol. Chem. **115** (1936), 435) and from the urine of pregnant mares (*Winterstein*, *Schwenk* and *Whitman*, Proc. Soc. Exp. Biol. Med. **32** (1935), 1087), and seems to be the true follicular hormone, oestrone being a secondary or transformation product.

Isolation of the *corpus luteum* hormone. — Progesterone can be extracted from fresh corpora lutea with lipoid solvents; it is found in the fractions soluble in benzene, acetone and methyl alcohol, and is enriched in the alcoholic phase by distribution between 33 % alcohol and light petroleum. In the crude state it is sensitive to alkali and oxidising agents, but being a neutral substance it can be freed from acid impurities by shaking the ethereal solution with $NaHCO_3$ for a short time (*Allen*, Am. J. Physiol. **92**, 174; **100**, 650; **106**, 55; *Fevold*, *Hisaw* and *Meyer*, Am. **52**, 3340; *Fevold*, *Hisaw* and *Leonard*, Am. **54**, 254). *Butenandt*, *Westphal* and *Hohlweg* (Z. physiol. Chem. **227**, 84) were able to prepare pure crystallisates with corpus luteum activity on the basis of the fact that almost the whole of the activity of the purified extracts is thrown down by the addition of semicarbazide: cautious hydrolysis of the slightly soluble crude semicarbazone, followed by sublimation in high vacuum, gave a crystallisate which contained 40 % of the activity of the original extract in a form stable to heat, acids and alkalis; this was a mixture of several closely-related substances, from which by systematic fractionation the physiologically active substance could be isolated. It is accompanied by an inactive saturated hydroxyketone, allopregnanolone, m.p. 194°, acetate m.p. 145°, oxime m.p. 223°, which is best removed by treatment with chlorsulphonic acid (*Butenandt* and *Westphal*, Ber. **69**, 443).

Progesterone, $C_{21}H_{30}O_2$ can be obtained in two polymorphic forms, prisms m.p. 128° and needles m.p. 121°; its dioxime melts at 243°. It is an unsaturated diketone and the position of the ultraviolet absorption band suggests that the one double bond is in the $\alpha\beta$ position to a carbonyl group. That the main skeleton is of the sterol type was shown by X-ray study of the crystals (*Neuhaus*, Ber. **67**, 1627). On this basis *Slotta* suggested the following formula which is closely related to that of pregnanediol (ibid. 1624).



Progesterone



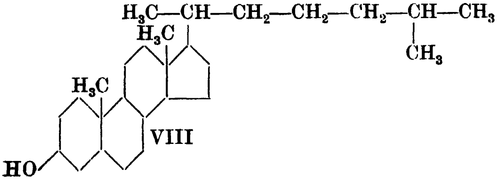
Pregnanediol

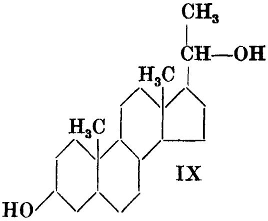
This formula has been fully established by the preparation of progesterone from two compounds of known structure, pregnanediol (*Butenandt* and *Schmidt*, Ber. **67**, 1901) and stigmasterol (*Butenandt*, *Westphal* and *Cobler*, ibid. 1611; *Fernholz*, ibid. 1885, 2027). The hormone differs from those described above in that it is only effective in relatively enormous doses.

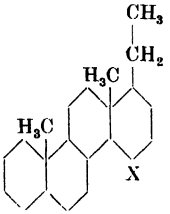
3) THE RELATIONSHIP OF THE SEX HORMONES TO EACH OTHER AND TO THE STEROLS.—PREGNANEDIOL

The constitutional formulae of the chief sex hormones being known, there arises the question of their relation to one another and to the sterols (p. 547). The formula of coprosterol and dihydrocholesterol, $C_{27}H_{48}O$, is shown by formula (VIII); comparison with the structural formulae for androsterone and oestrone shows that the same carbon skeleton is present in each, and that by replacement of the side-chain of eight C-atoms in these sterols by a keto-group a substance of the type of androsterone would be produced.

The relationship of the sex hormones to the sterols is shown in the case of androsterone by the intensive sterol colour reaction of its dehydro-compound, and with oestrone by the preparation of identical compounds from the hormone and from sterol derivatives.


VIII


IX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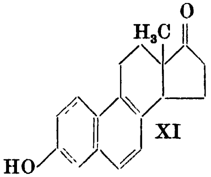

XI

Thus oestrone gives chrysene on energetic dehydrogenation, like cholesterol (p. 553) and cholic acid (p. 559), and the 1:2-dimethylphenanthrene (V) (p. 594) prepared from oestriol can also be obtained by the dehydrogenation of aetiobilianic acid (VI, p. 594) (*Butenandt*, *Weidlich* and *Thompson*, Ber. **66**, 601; *Butenandt* and *Thompson*, Ber. **67**, 140).

The question whether the sex hormones arise *in vivo* by side chain degradation of the sterols is so far unanswered; but a series of natural products is known which might be intermediate products in such a degradation (cf. Sterols, p. 552). This also holds for the bile acids (p. 549) and their derivatives, and especially for pregnanediol (IX), which accompanies oestrin in urine of pregnancy, and for the saturated hydroxy-ketone found with progesterone in the corpus luteum.

Pregnanediol, $C_{21}H_{36}O_2$, forms leaflets, m.p. 235°; it is only slightly soluble in almost all organic solvents and cannot be precipitated with digitonin. In the preparation of oestrone from urine of pregnancy, pregnanediol accompanies the oestrone until it reaches a high state of purity, and can then be separated because of its neutral character. Pregnanediol has the constitution (IX), and this formula is confirmed by the preparation of the fundamental hydrocarbon pregnane (X), m.p. 83·5°, from pregnanediol on the one hand, and from cholic acid (p. 559) on the other, by degradation of its side-chain to the residue $—CH_2·CH_3$ (cf. formulae, p. 596) (*Butenandt*, Ber. **63**, 659; **64**, 2529).

Since pregnanediol gives a positive iodoform reaction with alkaline iodine solution, one hydroxyl group must be in the side-chain; the other hydroxyl is in the first 6-ring, as is shown by the preparation of the keto-dicarboxylic acid, $C_{21}H_{32}O_5$, m.p. 270°, and its pyroketone, $C_{20}H_{30}O_2$, m.p. 147°. Pregnanediol diacetate has m.p. 180°.

Pregnanediol has so far been isolated only from urine of pregnancy, and it appears to be a neutral oxidation product of coprosterol and of lithocholic acid. Its empirical formula is very close to that of the physiologically inactive hydroxy-ketone mentioned above which accompanies progesterone prepared from corpus luteum. The diketones prepared from this hydroxy-ketone and from pregnandiol are not identical, because the former belongs to the cholesterol series and the latter to the coprosterol series, which differ in stereochemical configuration.

Pregnanediol, $C_{21}H_{36}O_2$, and the hydroxy-ketone, $C_{21}H_{34}O_2$, might clearly serve as intermediates between the bile acids and androsterone, and the former is very closely related to progesterone. The other hormones shown in the table on p. 593, equilin, hippulin and equilenin are dehydrogenation products of oestrone, the first two being isomeric with a total of four double bonds, and the last a naphthalene derivative (XI) with five double bonds.

So far only those hormones have been considered which have been well characterised by chemical methods (see table, p. 579). A short survey is now given of the more important animal hormones, the physiological actions of which are known, but which have not been prepared in the pure state and hence have not been fully investigated chemically.

Other endocrine glands which are known include the pituitary (hypophyse), the parathyroids, and the thymus gland; it is doubtful whether the pineal gland is an endocrine organ. The intestinal mucus and probably the heart also contain substances of specific physiological action, which may be considered as hormones.

The pituitary gland consists of three clearly defined parts, each of which is has a separate endocrine function; these are the anterior lobe, the median lobe and the posterior lobe of the pituitary.

F. THE HORMONES OF THE ANTERIOR LOBE OF THE PITUITARY (A.L.P.)

The A.L.P. is the site of formation of several hormones; it regulates the growth of the organism and the endocrine functions of most of the hormone glands.

1) THE GROWTH HORMONE

The connexion between the A.L.P. and the growth of the organism follows from clinical tests: increased activity of the gland causes acromegaly, recognised by an increase in the size of the anterior portions of the body, an enlarged jaw, hands and feet, coarsening and deformation of the face, tongue and larynx, as a result of the growth of the connective tissue and thickening of the epidermis; in juveniles the long bones of the extremities grow particularly rapidly (gigantism). Decreased action of the A.L.P. leads to dwarfed growth. — The results of animal experiments are in agreement with the clinical results: injury of the A.L.P. leads in young animals (dogs, rats) to interruption in growth and dwarfs (*Ashner*, *Smith*); the administration of A.L.P. extracts causes acceleration of growth, and to some extent giant growth, in planarians (turbellarians), tadpoles, axolotl, rats and dogs (*Wulzen*, *Uhlenhuth*, *Allen*, *Evans*).

Little is known of the chemical properties of the growth hormone. To prepare an active hormone extract, ox A.L.P.s are extracted for 10 mins. with 40% alcohol, rubbed to a paste with sterile sand and extracted with physiological salt solution. The hormone contained in this extract is precipitated from solution by the addition of alcohol; it is sensitive to heat and hydrolysing agents and is inactivated by digestive ferments (*Long* and *Evans*, Anat. Rec. **21**, 62; J. Amer. Med. Assoc. **101**, 425; *Evans* and *Simpson*, Amer. J. Physiol. **89**, 371).

2) THE PRIMARY SEX HORMONE (GONADOTROPIC HORMONE)

Besides the growth hormone, the A.L.P. contains a substance in the absence of which the sexual glands of both sexes cannot fulfil their functions; this "primary sexual hormone" is not specific for either sex, and it controls the development and functions of the gonads. The physiological significance of this gonadotropic hormone is clear from the following discoveries (*Smith* and *Engle*, *Aschheim* and *Zondek*, *Evans*).

(a) If the A.L.P. is removed from immature animals, they never attain sexual maturity. (b) When the A.L.P. is removed from mature animals, sperm production, egg-ripening and oestrus cease, the follicle in the ovary atrophies, new corpora lutea are no longer formed, but those already there are retained for some time; gradually complete atrophy of the genital organs and of the subsidiary glands of the genital tract takes place. (c) A.L.P.-ectomised animals of both sexes can be cured of these deficiency symptoms by the implantation of A.L.P.; in the female organism, enlargement and increase in weight of the ovaries takes place and new follicles and corpora lutea are formed, but it is difficult to stimulate the ovary to its full function again. In the male sex, complete regeneration takes place; the testes assume normal weight, and sperm production, libido and fertility return to normal. In both sexes an increased development of the secondary sex organs takes place parallel with the changes in the sex glands. If the experiment is interrupted, a complete reversal of the induced development follows. (d) The behaviour is equally clear when immature animals are implanted with A.L.P. tissue. It is possible to increase the size of the ovaries of an immature female rodent above a certain age 10 to 20 times, and to cause the formation of follicles and corpora lutea (luteinisation); changes occur which would normally appear days or weeks later. Parallel to the changes in the ovaries there occurs marked growth of the uterus and vagina together with the phenomena of heat. The immature male animal does not respond so clearly; changes of the testes and increased spermatogenesis can scarcely be observed, but the effect upon the development of the subsidiary glands is more obvious. (e) An important confirmation of these experimental results is the proof that no physiological action is obtained by implanting A.L.P. into castrated animals. From this fact it is a necessary consequence that the physiological function of the A.L.P. is the formation of the gonadotropic factors; as a result of its action the sex glands perform their normal functions, and all changes in the remaining sexual organs are induced secondarily by these.

The changes caused in the immature female rodent by the action of A.L.P. are so characteristic that they are used for the detection and quantitative estimation of gonadotropic activity. For example, on the basis of this test, the mouse-unit (M.U.) of gonadotropic hormone is the smallest quantity of substance which, on administration in a certain way (subcutaneously) to an immature female mouse, causes ripening of the follicle or luteinisation.

The gonadotropic substance has been extracted with solvents from the A.L.P. by *Evans*. This discovery is the prelude to a chemical investigation of the problem (Anat. Rec. 21, 62; 23, 19; Amer. J. Physiol. 80, 114; *Zondek* and *Aschheim*, Klin. Woch. 6, 248; 7, 831; Arch. Gynäk. 130, 1).

It is not known how many substances are present in the gonadotropic principle; it is commonly assumed that several material factors are concerned, of which one causes ripening of the follicle ("prolan A"), another the luteinisation ("prolan B"), but there is no clear proof of this assumption.

During pregnancy, the urine of women contains large quantities of gonadotropic hormone. The physiological detection of this excretion by means of an immature mouse can be used for the recognition of the first stages of pregnancy (*Aschheim-Zondek* reaction). The gonadotropic substance in the urine of pregnancy does not come from the pituitary, but from the placenta; it is, however, very probably identical with the hormone from the A.L.P., so that such urine is a valuable starting material for the chemical characterisation of the primary sexual hormone.

Properties. — The gonadotropic substance is soluble in water, dialysable, and sensitive to heat, hydrolysing agents and proteolytic enzymes; it can be adsorbed from acetic acid solution on to permutite, from which it can be eluted with ammonia. In contrast to the growth hormone, it can be precipitated by acetone from 50% alcohol, in which it is soluble. The purest sample obtained causes ripening of the follicle and luteinisation in the immature mouse in doses of 1 γ (*Dickens*, Biochem. J. **24** (1930), 1507; ***Marshall***, ibid. **26** (1932), 1358; **27** (1933), 621; *Zondek*, *Scheibler* and *Krabbe*, Biochem. Z. **258**, 102; *Fischer* and *Ertel*, Z. physiol. Chem. **202**, 83).

3) THE THYREOTROPIC HORMONE

A similar mutual relationship exists between the thyroid gland and the A.L.P. as between the sexual glands and the A.L.P. This is shown most clearly by experiments on the larvae of amphibians: if the pituitary is removed from the tadpole, its thyroid remains abnormally small and incapable of functioning, and as a result of the deficiency in thyroxin, metamorphosis does not take place. Minimal doses of an extract of A.L.P. causes normal growth and metamorphosis of the tadpole (*Allen, Evans, Smith*). In particular, it has been shown that under the action of A.L.P. extract the epithelial follicle of the thyroid gland is stimulated and the thyroid secretion set free. The thyroid gland of warm blooded animals also becomes smaller and incapable of functioning after removal of the pituitary; in young guinea-pigs the change of the thyroid gland into a functional gland under the action of A.L P. extracts can be readily followed histologically, and a reaction for the detection of the thyreotropic hormone has been based upon this (*Schöller* and *Junkmann*). The thyreotropic hormone can be separated from the growth hormone and the gonadotropic substance, but it has properties quite similar to these: it is sensitive to heat and to hydrolysing agents and is inactivated in the stomach and intestinal canal; it is readily soluble in water and in 50—70% alcohol, and insoluble in most organic solvents (*Paal*, Klin. Woch. **1921**, 2172; *Anselmino* and *Hoffmann*, ibid. 2380; *Junkmann* and *Scholler*, ibid. **1932**, 1176; *Janssen* and *Löser*, Arch. Exp. Path. **163**, 517; *Hohlweg* and *Junkmann*, Pflügers Arch. **232**, 148).

4) FURTHER HORMONAL FACTORS OF THE A.L.P.

It appears certain that the endocrine functions of the A.L.P. are not exhausted by serving as a source of the three hormones described above; many experimental results indicate that the remaining hormone glands are activated by endocrine stimulation from the A.L.P.; e.g. the A.L.P. influences the suprarenals, the "adrenotropic" factor of the A.L.P. causing increased excretion of adrenalin from them. Since adrenalin arrests the lowering of the blood sugar caused by insulin (p. 586), the adrenotropic factor of A.L.P. is known as the "contra-insulin hormone". In a similar way the A.L.P. activates the parathyroids and the pancreas, and the metabolism of fats and the secretion of milk are influenced by the A.L.P. These many secretions of the A.L.P., the presence of which has only been detected so far by biological experiments, have scarcely been characterised as chemical substances, and it cannot be decided whether or not all the distinct physiological actions are derived from different hormones (*Lucke*, Klin. Woch. **1932**, 1678; *Anselmino*, *Herold* and *Hoffmann*, ibid. **1933**, 1245; *Anselmino* and *Hoffmann*, ibid. 1435; *Anselmino*, *Herold* and *Hoffmann*, ibid. 1944; **1934**, 209; *Hoffmann* and *Anselmino*, ibid. 44; Arch. Path. Pharm. **170**, 166).

G. THE HORMONES OF THE POSTERIOR LOBE OF THE PITUITARY (P.L.P.)

Extracts of P.L.P. bring about the following pharmacological reactions: (1) they raise the blood-pressure; (2) they stimulate the contraction of the uterus; (3) they check diuresis; (4) they aid the secretion of milk; and (5) they increase intestinal peristalsis (*Schäfer* and *Oliver*, *Ott*, *Scott*, *Dale*).

The preparation of a pure biological principle from the P.L.P. has not yet been carried out, and the number of hormones produced is not yet known; hence there is no evidence as to how many substances cause the pharmacological actions of the P.L.P. extract. *Kamm* (1928) has conclusively proved that at least two incretes are present in P.L.P. extract. He extracted the tissue with 0·25% acetic acid, precipitated the biologically active principles with ammonium sulphate and took up the precipitate in 99% acetic acid; with ether or light petroleum he precipitated part of the substance dissolved in the acetic acid. Physiological tests showed that in this fractionation the uterine stimulant remained in solution; it was named oxytocin (α-hypophamine, orasthin). The precipitated component contained the blood pressure activity, the diuresis-checking and the intestinal peristaltic action. The substance with the action upon the circulation is known as vasopressin (β-hypophamine, tonephin). — Of the properties of the two substances all that it is known is that they are easily adsorbed and labile to alkali; they are more resistant to acids, but strong mineral acids destroy them (*Gulland* and *Newton*, Biochem. J. 26 (1932), 337).

H. THE HORMONE OF THE MEDIAN LOBE OF THE PITUITARY: INTERMEDIN

The presence of a hormone can be proved in the median lobe of the pituitary of cold and warm blooded animals; up to the present it has been characterised only by its action upon the pigment cells of fishes and amphibians: it causes the opening of all the pigment cells and is responsible for the adaptation of the colour of many animals to their surroundings. This hormone is known as intermedin; the role it plays in the higher vertebrates is unknown. Tadpoles with no pituitaries remain permanently pale, since the dark pigment cells (melanophores) cannot expand; frogs and toads without pituitaries lose the ability to adjust the colour of their skin to changes in the light, moisture and temperature. Administration of pituitary extract to these animals causes an immediate opening of the melanophores. The minnow (*Phoxinus laevis*) reacts to the administration of pituitary extract with a deep colouration, by the opening of the black and red pigment cells; in particular the opening of the red pigment cells (erythrophores) at the points of attachment of the breast-, stomach- and rear-fins is a specific indication of intermedin action, and serves as the basis for a specific test for the hormone: one phoxinus-unit of intermedin causes in three of five minnows a purple-red colouration 4—9 mm^2. in size at the points of attachment of the fins, and a linear shining purple-red colour behind the rear fin; the reaction lasts one hour.

Quantitative studies with the aid of this test have established that the greatest concentration of intermedin is present in the median lobe of the pituitary; except for the brain, no other organ contains intermedin (*Swingle*, *Hogben* and *Winton*, *Zondek*).

Properties of intermedin. — The hormone of the median lobe can be extracted from the gland with hot 0·25% acetic acid; it is stable to boiling, but is sensitive to fermentative digestion and to irradiation with ultraviolet light. It appears to be almost insoluble in ether, acetone and ethyl acetate, difficultly soluble in benzene and chloroform, and readily soluble in alcohol; it is dialysable. Acids and alkali destroy the activity only under energetic conditions. Thus intermedin is considerably different in its properties from all the other hormones of the pituitary, so that it is easy to separate from the other active substances of this gland (*Zondek* and *Krohn*, Klin. Woch. **405** (1932), 404, 1293).

I. THE HORMONE OF THE PARATHYROID GLANDS: PARATHORMONE

Removal of the parathyroids leads to a severe tetanus (*Tetania parathyreopriva*) which results in death; the symptoms are strong over-stimulation of the peripheral nerves, convulsions and violent contractions of the muscles. The cause of these symptoms lies in a break-down in the calcium metabolism: shortly after the exstirpation of the gland, the Ca content of the blood and tissues falls considerably and continuously; administration of lime and implantation of parathyroid gland combat the tendency to tetanic spasms (*v. Eiselsberg*, *Gley*, *Erdheim*, *McCollum*).

Collip (1925) was the first to prepare a definitely active extract from the parathyroid glands, thereby giving the final proof of the presence in the parathyroids of a hormone ("parathormone") which regulates the Ca metabolism of the organism. The extract has the following physiological properties. (1) In the normal dog it causes an immediate increase in the Ca content of the serum, the increase being proportional to the dose given; this action can be used as a quantitative test for parathormone: the unit is defined as 1/100th part of an extract which is necessary in one injection to raise the Ca content of the blood of a dog by 50% in 12 — 16 hours. (2) A complete substitution therapy can be carried out on the parathyroidectomised animal with the extract prepared by Collip; the low Ca level is raised to normal and the symptoms of tetanus vanish.

Hence the parathyroid glands are vital organs for animals and mankind; through their hormone they control the Ca level of the blood and thereby the normal development and maintenance of the bones.

Preparation of the active principle from the glands and its properties. — Fresh or frozen glands are extracted with 1·5—5% dil. HCl at 100° for $^1/_2$—1 hour, the solution is brought to p_H 8—9 by the addition of alkali, filtered and again acidified; at p_H 5·5 another precipitate appears. From the filtrate the parathormone is precipitated by the addition of common salt; purification is achieved by repeated precipitation of the active fraction at various p_H, giving a substance which contains one unit in 0.3 mg. — The substance is amorphous and not dialysable; it is soluble in water and in 80% alcohol, and insoluble in ether, acetone and pyridine; it gives all the usual protein reactions, and loses its physiological activity by an hour's boiling with 10% HCl, or 5% NaOH, and by digestion with trypsin or pepsin (*Berman*, Amer. J. Physiol. **75**, 358; *Allardyce*, ibid. **98**, 417; *Collip*, J. Biol. Chem. **63**, 395; *Collip* and *Clark*, ibid. **64**, 485; **66**, 133).

J. THE THYMUS AND PINEAL GLANDS AS ENDOCRINE ORGANS

Our knowledge of the endocrine functions of the thymus gland and the pineal gland (epiphyse) is very imperfect.

Judged from its anatomical relationships, the thymus gland should be of chief significance in its influence on the young growing organism, since the gland reaches its highest stage of development at about puberty and then gradually degenerates. The results of thymus extirpation appear to be to some extent contradictory, but it is particularly interesting that disturbances of the skeletal growth, of the normal genital development and of the nervous system can be observed in young animals. An influence of the thymus substance, which could definitely be reproduced, upon the growth and development of young animals was found by *Gudernatsch* in experiments with frogs' larvae: the thymus-substance when fed to tadpoles caused retardation of the metamorphosis and giant growth, that is, actions opposite to those of thyroxin. — Scarcely anything is known of the chemical properties of the thymus hormone (*Asher* and *Nowinski*, Biochem. Z. **226**, 415; *Asher* and *Stotzer*, ibid. **234**, 1; *Asher* and *Zenklusen*, ibid. **252**, 309; *Asher*, ibid. **257**, 209).

Our knowledge of the endocrine function of the pineal gland is still more imperfect; see the summary in "Endocrinology" 7, 379; *Silberstein* and *Engel*, Klin. Woch. **1933**, 908; *Engel*, ibid. **1934**, 266.

K. THE HORMONE OF THE INTESTINAL MUCUS: SECRETIN

Bayliss and *Starling* (1902) prepared from intestinal mucus an extract that stimulated a lively secretion from the pancreas when administered parenterally; hence it was named secretin. To prepare a highly active concentrate the active substance can be adsorbed from an alcoholic extract of intestinal mucus on to the salt of a bile acid; 0·03 mg. of the purest preparation stimulates in cats the secretion of 2 cc. of pancreatic juice. Secretin has the properties of a polypeptide; its physiological action is completely destroyed in a short time by digestion with trypsin and pepsin and by heating to 100° (Proc. Soc. exp. Biol. **111**, 429; *Cunningham*, Biochem. J. **26** (1932), 1081).

L. THE HEART AND CIRCULATORY HORMONES: CALLICREIN

Löwi and *Haberlandt* have extracted from the heart a substance which has an action similar to adrenalin, accelerating the heart and increasing the intensity of the beat. It is uncertain whether his substance is a new chemical compound. — A substance which has been more fully investigated is a "circulatory hormone" first prepared by *Kraut* and *Frey* from urine; it appears to be widely distributed in the body, but is probably formed in the pancreas. This hormone is named callicrein, and its effect is shown in a characteristic distribution of the blood: the vessels of the lungs, brain, muscles and skin are enlarged, hence these organs become full of blood, and at the sime time the heart is stimulated to increase its frequency and amplitude of beat.

In the preparation of callicrein-concentrates from urine, serum or tissues, use is made of its solubility in water, its precipitation with lead acetate, uranyl acetate, and phosphotungstic acid, and its ease of adsorption by aluminium hydroxide. The callicrein unit is that quantity of substance contained in 5 cc. of mixed urines; the purest preparation contains the unit in 0·1 mg.; it shows no protein reactions, and is extremely sensitive to heat, acids and alkali. The property of callicrein which is most interesting from a physiological point of view consists in its rapid inactivation by a specific substance in the blood serum, which can be destroyed by boiling or by the addition of alcohol or strong acids. The inactivator does not destroy callicrein, but forms an inactive compound with it, from which the hormone can be regenerated merely by displacing the p_H to the acid side. The inactivator probably belongs to the polypeptide group; it can be purified so far that 6γ of the best preparation inactivates 1 unit of callicrein. It is probable that an equilibrium, dependent upon the p_H of the serum, exists between the inactive compound (callicrein + inactivator) and its two components; in this way it appears possible that even small changes in the p_H of an organism exert a regulating influence upon the circulation by means of the amount of callicrein which is free or combined (*Frey*, Z. angew. Chem. **43**, 1120; *Frey*, *Kraut* and *Werle*, Klin. Woch. **1932**, 846; *Frey* and *Werle*, ibid. **1933**, 600).

M. PLANT HORMONES — PHYTOHORMONES: THE AUXINS

It is of great significance that recent experimental work has shown that the plant organism also produces active substances, whose functions correspond to those of the animal hormones; that such substances exist was postulated fifty years ago from a theoretical standpoint by the plant-physiologist *Sachs*. Growth and growth movements, and probably also root and flower formation and diametral growth of plants, take place as a consequence of the presence of physiologically active substances which are produced in the plants (cf. Analyse der Pflanzenhormone in *Klein*'s Handbuch der Pflanzenanalyse, Berlin 1933, p. 1005).

Only one group of plant hormones has been investigated in detail by chemical methods; this is the group of the auxins, which are discussed below.

Physiology. — New plant cells are formed by division at the growing tips; this cell-division causes but a slight increase in volume, which is a consequence of the process of cell-extension. The latter occurs under the influence of the auxins, as has been shown by observations on the growth of grass seedlings. If an oat seedling is decapitated, its growth ceases; if the tip is replaced, the growth begins afresh, but not if a piece of tinfoil is placed between the two pieces of the plant. The growth effect can also be observed with the tips of the seedlings of other plants and species, but cylindrical pieces cut from the base of the seedling produce no growth. The effect observed is due to the growth hormone auxin, which is produced in the growing tip and transported downwards. If the tip is attached to the side of the seedling, the shoot grows in a curve, since one side obtains more growth substance than the other. Light and gravity influence the direction of flow of the growth hormone; it becomes more concentrated on the shady side and also on the side towards the earth, and this distribution of the growth substance is the cause of the phenomena of phototropism and geotropism. Auxin can be extracted from the tips of oat-seedlings by placing them upon 3% agar-agar; the growth hormone diffuses into the agar plates, which are now capable of causing the growth of decapitated oat-seedlings (*Boysen-Jensen, Paal, Went*).

Test for auxin. — An agar plate containing auxin placed laterally on a decapitated oat-seedling causes a bending of the seedling proportional to the quantity of hormone present. One unit of auxin causes the decapitated seedling to bend through 10°.

Isolation. — The chemical investigation of the auxins is due to *Kögl* (*Kögl*, N. **21**, 17; *Kögl, Haagen-Smit* and *Erxleben*, Z. physiol. Chem. **214**, 241; **216**, 31; **220**, 137; *Kögl, Haagen-Smit* and *Tönnis*, ibid. 162; *Kögl*, Z. angew. Chem. **46**, 469; **47**, 359). Male urine, maize-germ oil, malt and yeast were used as sources for the preparation of the active pure substance; in the isolation advantage was taken of the solubilities and of the fact, which was soon recognized, that the auxins are acids. So far, four auxins have been isolated in the pure state:

(1) Auxin a, $C_{18}H_{32}O_5$, m.p. 196°, from urine, maize-germ oil and malt; contains 50 thousand million units per gram.

(2) Auxin b, $C_{18}H_{30}O_4$, m.p. 183°, from maize-germ oil and malt; it has the same activity as auxin a.

(3) Auxin-lactone, $C_{18}H_{30}O_4$, m.p. 173°, from urine; it has the same activity as a and b.

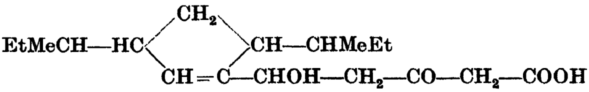
(4) Heteroauxin, identical with β-indolyl-acetic acid (vol. IV), from urine and yeast; its activity is only 25% of that of auxin a.

The constitution of auxins a and b. Auxin a is an unsaturated monocyclic trihydroxy-carboxylic acid and contains one double bond; auxin b is an unsaturated monocyclic hydroxy-keto-carboxylic acid and also contains one double bond; the constitutions of the two substances are as follows:

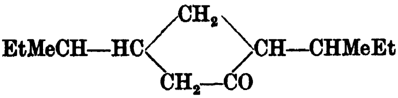
Auxin a: $C_{13}H_{23}$—CH(OH)—CH_2—CH(OH)—CH(OH)—COOH
Auxin b: $C_{13}H_{23}$—CH(OH)—CH_2—CO—CH_2—COOH.

The auxin-lactone is probably the δ-lactone of auxin a.

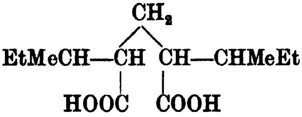
The most probable constitutional formula for auxin b,



has been deduced from the following experimental results: dihydroauxin a, m.p. 199°, is oxidised by CrO_3 in acetic acid to an optically active neutral compound, a cyclic ketone, $C_{13}H_{24}O$; it corresponds to a dicarboxylic acid, $C_{13}H_{24}O_4$, m.p. 129°, which is obtained from the unsaturated auxins with $KMnO_4$, and must be regarded as a substituted glutaric acid from its behaviour in the Blanc reaction.



Cyclic ketone $C_{13}H_{24}O$



Dicarboxylic acid $C_{13}H_{24}O_4$.

Kögl and *Erxleben* (Z. physiol. Chem. 227, 51), although they had only 90 mg. of this acid, succeeded in proving its constitution by dibrominating it and hydrolysing to a dihydroxy-acid; the methyl ester of this was treated with MeMgI, and oxidation of the resulting glycol gave a diketone, which from its behaviour must be a 1:3-diketone. Alkali fission gave α-methyl butyric acid and 3-methyl-pentanone-2, so that the dibasic acid must be symmetrical and have the formula shown above. This degradation shows the presence of the characteristic isoprene branched chains in auxin.

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